JUL 6 1939

VOL. XXXII. NO. 8 JUNE 1939

Medical Library

PROCEEDINGS *of the* ROYAL SOCIETY OF MEDICINE

LONGMANS, GREEN & Co LTD
39 PATERNOSTER ROW, LONDON
NEW YORK · BOMBAY · CALCUTTA · MADRAS

All rights reserved

ANTUITRIN 'S'

(ANTROIDIN)

A solution of the anterior-pituitary-like sex hormone derived from pregnancy urine

ANTUITRIN 'S' contains the "anterior-pituitary-like sex hormone," which consists of a luteinizing hormone and a smaller quantity of follicle-stimulating hormone.

THERAPEUTIC INDICATIONS

FEMALE: Functional uterine bleeding, amenorrhoea and oligomenorrhoea. Dysmenorrhoea. Habitual or threatened abortion.

MALE: Cryptorchidism. Impotence. Aspermia.

EITHER SEX: Delayed puberty. Genital infantilism. Frohlich's syndrome (adipose-genital dystrophy). Acne vulgaris. Sterility.

Antuitrin 'S' is standardized to contain 100 rat-units per c.c. and is issued in rubber-capped vials of 10 c.c., also in vials of 5 c.c. containing 500 rat-units per c.c. A comprehensive brochure describing the properties of Antuitrin 'S' is available to members of the medical profession on request.

Parke, Davis & Co., 50 Beak St.

LONDON, W.1.

Laboratories: Hounslow, Middlesex. *Inc. U.S.A., Liability Ltd.*

Section of Therapeutics and Pharmacology

President—J. W. TREVAN, M.B.

[*March* 14, 1939]

DISCUSSION ON VITAMIN E

Professor J. C. Drummond: It was a great surprise to nutrition workers when, some fifteen years or so ago, H. M. Evans and his colleagues [1], Mattill [2] and Sure [3] independently announced the discovery of a new member of the fat-soluble group of vitamins. At the time many were sceptical, but it was not long before the evidence of differentiation from the recognized vitamins A and D was accepted. In studies on rats it was found that diets deficient in vitamin E, as it was labelled, resulted in the production of two abnormal conditions, both affecting reproduction. In the female no disturbance of the reproductive cycle was detected until pregnancy was well advanced, but there then occurred the death of the embryos followed by resorption. This form of sterility could be prevented by administering in the earliest stages of pregnancy adequate amounts of foods containing vitamin E. In male rats deficiency of this vitamin was followed by slow but steady degeneration of the testicle, and in this case regeneration was found to be exceedingly difficult to bring about. Advanced cases of degeneration could not be improved by an adequate diet, while mild cases responded only slightly after months of special treatment with materials rich in E.

In the last year or two there has been a remarkable burst of activity in research on the nature and function of vitamin E or, one should say, the vitamins of the E group, for there are probably three, all closely related chemically. Perhaps the most striking achievements of this work have been the isolation of these vitamins in a chemically pure condition, the elucidation of their chemical constitution and the synthesis of important members of the group. As a class of compounds they are generally known among chemists to-day as the tocopherols. The synthesis of α d–l tocopherol is now carried out on an industrial scale, thus providing material of certain potency for clinical use.

Unfortunately, physiological studies have as yet provided nothing more substantial than a great many negative results. Some of these are important, but they do not yet provide an adequate background against which we can begin to build a plausible theory of the action of the vitamins. One thing seems certain: The anterior pituitary is involved. This is by no means a new idea; Verzár and his collaborators suggested some eight years ago that the condition of vitamin-E deficiency resembled in some respects that associated with hypophysectomy [4]. Their evidence was slender, it is true, but it clearly pointed the way for further study. Attention was diverted

for a time from this path because H. M. Evans could not reconcile the apparent maintenance of ovarian structure and function in the female rat and the steady degeneration of the testicle in the male with anterior pituitary failure [5].

Nelson, however, brought attention back to the hypophysis when he showed in 1933 that E deficiency in the male is associated with changes in the anterior lobe similar to but less marked than those seen after castration [6]. He also found a related increase in the gonadotrophic potency of glands from E-deficient male animals.

Working in collaboration with Dr. M. D. Wright of the Vitamin Research Laboratories, Hammersmith, and Dr. R. L. Noble of the Courtauld Institute of Biochemistry, Middlesex Hospital, I have confirmed this interesting observation. We did not find, as McQueen-Williams claimed, that glands from the female E-deficient animals show the same change [7]. Indeed, as some of our results indicate, the female glands seem to show reduced gonadotrophic potency after long periods of E deprivation.

Implantation of One Pituitary Daily for Five Days into Immature Rats.

Source of Implant	Weight grm.	Uterus mgm.	Ovaries mgm.
E-deficient ♂	60	73	63
Control 1	56	100	43
Control 2	52	73	42
E-deficient ♀..	53	30	7
Control 1	50	41	9
Control 2	56	73	11

Implantation of Two Pituitaries for Five Days into Hypophysectomized Immature Does.

Source of implant	Uterus mgm.	Ovaries mgm.
♀ on stock diet	56	137
♀ after 3 months' E deprivation ..	45	84
♀ after 12 months' E deprivation ..	44	42

In another experiment of this latter type we found the male E-deficient glands to be more than five times as active in promoting ovarian development as those from females.

A year or two ago Miss Singer, working in my laboratory and in collaboration with Dr. Rowlands of the National Institute for Medical Research, found by using the rabbit-ovulation test that the hypophysis of E-deficient female rats exerted considerably less luteinizing action than those of normally fed animals. Administration of vitamin E restored the gland to a normal condition.

These observations, taken together with the valuable studies of Miss Barrie, about which she will herself speak later, strongly suggest that E deficiency is associated either with a general depression of pituitary function or with a disturbance of the normal pituitary hormone balance [8]. To both these possibilities Dr. Wright, Dr. Noble, and I have given some attention.

The testicular degeneration seen in E deficiency might indicate either condition, for atrophic changes are associated both with hypophysectomy and with the effects of long-continued treatment with œstrone. Actually, however, our studies reveal that the condition of the testis is not the same in all these cases. It is rather characteristic of E deficiency that the large majority of the tubules show complete disorganization and degeneration of all spermatogenic cells. Very few tubules with any vestige of normal structure remain. The interstitial tissue appears to be relatively unaffected,

although there is evidence that after long periods of deficiency the accessory organs show definite signs of atrophy. This is supported by the observations of Bacharach and Wiesner on sex behaviour as affected by E deprivation [9]. Hypophysectomy, on the other hand, produces complete degeneration of testicular structure, and repeated administration of œstrone, while it may profoundly affect the weight of the testes, does not produce histological degeneration comparable with that seen in E deficiency.

The most striking fact about the degeneration following E deficiency is that it is impossible to effect a restoration of spermatogenesis by administering vitamin E in a manner similar to that in which one can bring about recovery after hypophysectomy by giving anterior pituitary extracts or implanting the glands.

Following up this line of approach we have attempted to regenerate the testes of E-deficient rats by administering extracts from pregnant mare's serum (antex or antostab), either alone or reinforced by vitamin E given orally in large doses. In another experiment the influence of the administration of pregnancy-urine extracts (physex) was also studied. The results were uniformly negative.

E-deficient ♂ rats (200 *days deficiency*).

Dosage	Weight grm.	Weight fresh testis grm.	Weight testis per 100 grm. weight
Nil	260	2·86	1·1
	287	3·12	1·08
	238	2·50	1·09
5 mgm. E daily for 14 days	250	1·97	0·79
	198	1·98	1·0
	160	2·53	1·58
10 M.U. antex for 14 days	240	2·93	1·23
	300	2·93	0·97
	240	2·17	0·90
10 M.U. antex + 5 mgm. E for 14 days	230	2·30	1·0
	225	1·86	0·82
	135	1·15	0·76
Nil	290	1·10	0·39
	220	1·54	0·69
5 M.U. antex + 5 M.U. physex	240	1·08	0·45
	260	1·04	0·40
5 M.U. antex + 5 M.U. physex + 5 mgm. E	256	1·12	0·44
	255	1·14	0·44
10 M.U. antex + 10 M.U. physex	257	1·44	0·56
	297	0·97	0·35
	260	0·82	0·31

Attempts to regenerate the testicles in rats which had been deprived of E for a shorter period (150 days) by giving very heavy dosage with the vitamin before administration of antex also failed. The animals were given a diet containing 12% of an active wheat-germ oil and, in addition, 25 mgm. of an E-rich concentrate daily for 36 days, after which they received daily injections of 20 M.U. antex for 24 days. There was no significant increase in the weight of the testicles.

When we turn to the effect of E deficiency on the ovary, we fail to find any evidence of atrophy. Moreover, such ovaries respond, although not quite as strikingly as do those of normal animals, to administration of antex. The following figures give the mean ovarian weights in an experiment of this type.

	Treatment	Mean weight of rat grm.	Mean weight of ovaries mgm.	Mean weight (mgm.) ovaries per 100 grm.
Normal	Nil	140	46	33
E deficient	Nil	120	39	32
Normal	5 M.U. antex for 5 days, then 20 M.U. antex for 5 days	155	122	77
E deficient	Ditto	168	84	50

Shute's interesting view that the condition of vitamin-E deficiency in female rats, and also in women, is associated with the presence in the serum of a substance resembling œstrin is in line with the idea of a hormonal imbalance, but it appears that his experimental work requires confirmation [10]. It is a view that at first appears reconcilable with the termination of pregnancy in the rat on or after the fifteenth day. But if this symptom of E deficiency is attributable to the long-continued and dominating influence of an œstrin-like factor, there are other facts which are not in accord. One is the peculiar type of testicular degeneration, another is that the size of the ovaries is unaffected, and a third is the absence of any change of weight in the pituitary gland in prolonged E deprivation.

Following the line of argument that the gestation-resorption characteristic of the condition of E deprivation is caused either by a general pituitary deficiency or, more probably, by a faulty hormone balance, my colleagues and I have attempted to prevent its occurrence in female rats by various procedures, all of which were without the slightest obvious beneficial effect. They were: (*a*) Injection of a saline suspension of dried anterior pituitary equivalent to 5 mgm. of gland a day; (*b*) implantation of fresh pituitary glands from normal rats, two glands being given on alternate days throughout pregnancy; (*c*) injection daily during pregnancy of 10 M.U. of antostab (pregnant mare's serum extract); (*d*) injection of 5 M.U. daily of physostab (extract rich in luteinizing factor); (*e*) implantation under the skin of 5 mgm. of progesterone and, finally (*f*), implantation of 20 mgm. of testesterone. In every case death and resorption of the litter occurred. In view of these negative results we are unable to suggest what type of hormonal disturbance is responsible for the abnormalities of the reproductive system seen in E deficiency, nor are we yet in a position to express an opinion whether the pituitary is primarily involved or whether the changes in that gland are produced indirectly.

REFERENCES

1 Evans, H. M., and Bishop, K. S., *Science*, 1922, **56**, 650.
2 Mattill, H. A., *J. Biol. Chem.*, 1922, **50**, 54; 1923, **55**, 443.
3 Sure, B., *ibid.*, 1924, **58**, 693.
4 Verzár, F., and Kokas, E., *Pflüger's Arch. f. d. ges. Physiol.*, 1931, **227**, 511; also Verzár, F., Arvay, A., and Kokas, E., *Biochem. Ztschr.*, 1931, **240**, 19.
5 Evans, H. M., *J.A.M.A.*, 1932, **99**, 469.
6 Nelson, W. O., *Anat. Rec.*, 1933, **56**, 241.
7 McQueen-Williams, M., (1934), *Proc. Soc. Exper. Biol. and Med.*, **32**, 296.
8 Barrie, M., *Nature*, 1937, **139**, 286, **140**, 426; *Lancet*, 1937 (ii), 251.
9 Wiesner, B. P., and Bacharach, A. L., *Nature*, 1937, **140**, 97.
10 Shute, E., *J. Obst. & Gynæc. Brit. Emp.*, 1935, **42**, 1071; *Am. J. Obst. & Gynæc.*, 1937, **37**, 429.

Mr. A. L. Bacharach: Vitamin E was first discovered independently in three laboratories in the United States by the effect of its absence on reproduction in the albino rat. Like other vitamins, it is defined in terms of the effect that led to its discovery. Attempts to prove that the presence or absence of vitamin E is responsible for other phenomena in the rat, or in any other species, depend upon establishing a correlation between those phenomena and the property that led to its discovery and by means of which it is defined.

It is to be feared that a number of the alleged consequences of vitamin-E deficiency, and possibly some of the effects attributed to its addition, described in the literature of the subject, have been claimed without due regard for this consideration. When the addition of wheat germ oil has been followed by some observed phenomenon, this has occasionally been taken as proof that vitamin E caused the phenomenon. In some instances, as, for example, the presence in vitamin-E-deficient adult animals of the silky coat characteristic of the young, reported by Verzár as occurring in his rats, there has been a failure of all other investigators to repeat the observation. This suggests either that the effect was not connected with vitamin E as such, but with the absence of some unidentified factor, or that the phenomenon is confined to certain strains of experimental animals and cannot therefore be regarded as a fundamental property of vitamin E.

On the other hand, we have the finding of Thomas, Cannon, and their colleagues, at Iowa, that vitamin E appears not to be needed by the goat. Their work does not, it should be pointed out, involve abandonment of the description " antisterility vitamin " for vitamin E, provided we remember the original definition, which was in terms of the albino rat. As far as I am aware, every experiment properly conducted with this variety of animal has confirmed the phenomena originally observed by Evans, by Mattill, and by Barnett Sure, with their respective collaborators. The qualitative detection of vitamin E depends on reproducing the phenomena by which it was detected ; its quantitative determination must, ultimately, depend upon using these phenomena in the form of a response that is graded to the dose of the vitamin-containing material under test. For this purpose, the prevention of gestation-resorption in the mature albino rat receiving a diet devoid of vitamin E has been most generally used, but there do not appear to have been any publications on quantitative methods other than those of Palmer (1937) and of Bomskov (1938), and those of my colleagues and myself (1937, 1938*a*, 1938*b*).

100% of the gestation-resorptions characteristic of vitamin-E deficiency can be obtained when young rats at weaning, without any special " running out " treatment of their mothers, are placed upon a suitable vitamin-E-free diet. This 100% sterility has been produced in many hundreds of rats for a period of more than two years. Further, when young animals at weaning are fed exclusively upon this diet supplemented with sufficient vitamin E, 100% fertility is secured.

A female rat raised on this diet is taken at the first or an early œstrus, as detected by examination of vaginal smears, and mated with a male of proved fertility ; the subsequent career of the mated animal has been discussed elsewhere and diagrammatically illustrated (Bacharach *et al.*, 1937). Only animals showing positive mating and implantation of embryos can be used in the test.

With groups of such animals we have been able to show that, provided the numbers used were adequate, the percentage of live litters following the administration of vitamin E is a function of the dose (Bacharach, 1938*b*). The relationship between percentage response and dose is found to be expressed by a curve of the usual sigmoid type, though the bottom limb of the S is hidden, owing to the relatively small number of animals that have in practice to be used. Following the principles laid down by Gaddum and others, the percentage response can be expressed as its normal equivalent

deviation, or as the " probit " of Bliss, and plotted against the logarithm of the dose, when a straight-line relationship should obtain. The extent to which the experiment results approximate to this linear relation is shown in fig. 1. The regression line is given by the equation

$$y = 0{\cdot}87x + 3{\cdot}87$$

y being the probit and x the logarithm (to base 2) of the dose ratio ; the relation between probits and logarithms of doses does not significantly depart from the linear. The relationship of probit to $\log_2$ dose can be expressed as an equation from which the percentage response to a given dose may be used to calculate the dose required to give a 50% response. With quantal or " all or nothing " responses of the type here

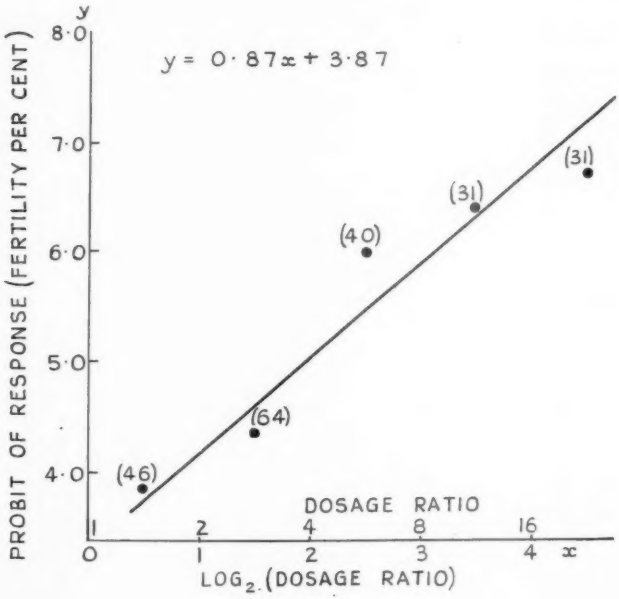


FIG. 1.

involved, comparisons at a level of 50% response keep the error, always large, as low as possible.

The fairly steep nature of the response curve, though it tends somewhat to increase the accuracy of quantitative comparisons, limits the utility of the test, because it increases the risk that a test dose chosen at hazard may produce a response lying above or below the part of the curve associated with reasonable accuracy.

The facts just summarized seem to be little appreciated by some workers in this field. In a recent paper an apparently lowered effect, when the dose of a particular substance was more than doubled, is completely ignored, while a corresponding difference of effect in the opposite direction, shown by two different substances, is taken to indicate a difference in biological activity.

These questions are of more than academic importance to medical science if vitamin E has a role in clinical and veterinary practice. We know that there exist certainly two, and possibly three, different forms of vitamin E in natural products; Karrer states that synthetic compounds related to the tocopherols have similar, if lower, activity. The chemical relationship between *a*-tocopherol and some of these compounds, for which Karrer has proposed the name " tocols ", is shown in fig. 2.

Natural *a*-tocopherol is dextro-rotatory; the synthetic product is racemic. Examination of the literature does not reveal any evidence making clear the relative activities of the natural and the lævo forms which, in equal quantities, constitute the synthetic racemic mixture.

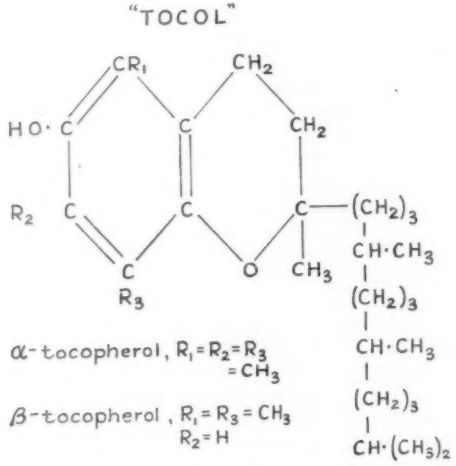


FIG. 2.

It is desirable to settle with some clarity the relative activities of synthetic racemic *a*-tocopherol, and the different naturally occurring forms of vitamin E. There are at the present time under investigation three chemical or physico-chemical tests for the tocopherols, all of them based upon the fact that the phenolic or quinol group of the substituted " tocols " is fairly easily oxidized. The substituted " tocols " also have characteristic absorption spectra. The measurement of the ultra-violet absorption at its maximum, together with the application of one or more of the tests just mentioned, may afford useful indications of the amount of tocopherol present in natural substances and medicinal preparations, but will not give an indication of the total vitamin-E activity unless it should prove that there is no quantitative difference between the two isomeric forms of *a*-tocopherol and any other naturally occurring physiologically active relatives.

My colleagues and I have attempted to improve methods for quantitative comparison of sources of vitamin E, so that, when an international standard

preparation and a unit based thereon become available, they can be brought into use as rapidly as possible, for purposes of standardizing medicinal preparations and of evaluating the vitamin-E content of natural raw materials. The need for such standardization is apparent when one looks at the literature, and particularly at the clinical literature, of vitamin-E studies. None of those clinical trials conducted on a reasonably large number of cases has been carried out on material that could be in any sense described as biologically " assayed ", for without a standard and a unit, there can be no true assay. Some of the samples of wheat germ oil or concentrate used have, it is true, been biologically " tested ", which means that they have been shown, on anything from one animal upwards, to possess vitamin-E activity. Study of the variance of animals submitted to vitamin-E dosage makes it clear that such tests could justify the description " satisfactory " for oils varying in vitamin-E content by a range of several to one. For this reason the absence of biologically assayed, or even adequately tested, material from most clinical tests on vitamin E rather heavily weights the scales against its use in therapy. It is to be hoped that the progress now being made will lead to a replacement on the market of unstandardized products by material for which at least some kind of quantitative information, however approximate, is available. There are signs that this change is already within the sphere of practical therapeutics.

It must be emphasized that observations made in the course of work carried out to improve quantitative measurement of the vitamin should only be applied with caution to the interpretation of physiological and pathological processes in other species of animals or even in the test species. It is with this reservation that I would like to report certain observations that seem, in some ways, to supplement observations made by other investigators.

We have found that the effects of a gestation-resorption do not show the simple reversibility implied or reported in the literature of the subject. Those animals that have had a single gestation-resorption appear to differ in two respects from virgin animals kept upon the same vitamin-E-free diet for the same time. First, they appear to offer greater obstacles to the implantation of fertilized ova, for the percentage of such animals failing to show the characteristic placental sign is greater than the corresponding percentage of virgins. Secondly, we find that the dose of vitamin E necessary to bring about 50% fertility in a group of animals that have already undergone a single gestation-resorption is from four to ten times greater than that required to bring about the same fertility rate in the virgins. These results point to some fundamental disturbance in the maternal organism, quite apart from the effect of vitamin-E deficiency on fœtal development; they are consistent both with the established occurrence of various types of endocrine disorder, as described by Barrie (1937) and by Rowlands and Singer (1936), and also with the pigmentary and histological changes in the uterine musculature, discussed by Martin and Moore (1938). Nevertheless, it is only fair to point out that Mason has not been able to confirm either of our own observations as to the effect of a resorption-gestation on fertility after a subsequent mating.

The connexion of vitamin E, through its effect on male and female reproductive systems, with the whole endocrine mechanism, especially that of the anterior lobe of the pituitary, offers a large field for research, only the outer edges of which have yet been even prospected. Even should the more optimistic hopes for the use of vitamin E on human, bovine, and other abortants prove in practice to have been based upon an incorrect interpretation of the experimental and clinical results so far obtained, fundamental study of the effects of vitamin E upon the experimental animal, if conducted with a proper appreciation of the quantitative aspects of the problem, must bring about results of scientific value and of importance to medicine.

REFERENCES

BACHARACH, A. L., ALLCHORNE, E., and GLYNN, H. E. (1937), *Biochem. J.*, **31**, 2287.
BACHARACH, A. L., and ALLCHORNE, E. (1938*a*), *ibid.*, **32**, 1298.
BACHARACH, A. L. (1938*b*), *ibid.*, **32**, 2017.
BARRIE, M. M. O. (1937), *Lancet*, 233, 251.
BOMSKOV, C. (1938), *Arch. f. exper. Path. u. Pharmakol.*, **190**, 627.
MARTIN, A. J. P., and MOORE, T. (1938), *Chem. & Ind.* (*Proc. Biochem. Soc.*), **57**, 973.
PALMER, L. S. (1937), *J. Ind. Eng. Chem.* (Anal. Ed.), **9**, 427.
ROWLANDS, I. W., and SINGER, E. (1936), *J. Physiol.*, **86**, 323.

Miss M. M. O. Barrie: *Vitamin-E deficiency in the rat.*—Vitamin-E deficiency is particularly interesting because it has been found that in experimental animals the effects of a partial lack of the vitamin are far more disastrous to the health and well-being of the animals than those produced by total deficiency. On first consideration this may seem unreasonable, but when one realizes that this vitamin is necessary for the normal course of pregnancy ending with the production of a normal living litter at term, and that without vitamin E resorption of the fœtuses takes place at an early stage in gestation, then it is easily seen that partial deficiency may have very severe consequences ; one would expect it to lead to resorption of the fœtuses at a later stage or to the delivery of dead young, and this is in fact the case.

A partial deficiency of vitamin E during pregnancy may result in (*a*) the production of a toxæmia of pregnancy, (*b*) the prolongation of gestation, or (*c*) deficiency of vitamin E in the milk, which causes abnormal development of the suckling young.

Let us consider first the toxæmia of pregnancy. This occurs in approximately 19% of rats which have been fed on a vitamin-E-free diet long enough to ensure sterility and then given a small but inadequate dose of vitamin E on mating (Barrie, 1939). The toxæmia is an easily recognized condition ; the affected animals become weak and crouch in a corner of their cage in obvious discomfort ; within twenty-four hours of recognition of the symptoms, severe cases are found bleeding from the nose and rectum, and death occurs during the next day. The chief histological findings in such animals are the marked kidney changes. In many cases the tubules are filled with albumin-like material and there are numerous stones, particularly round the peripheræ of the medulla. The kidney surface is pitted. In many animals there is fatty infiltration of the liver. Since these animals are not completely deficient in vitamin E, it may be presumed that the cause of the toxæmia is either the resorption of large amounts of fœtal material, or the toxic effect on the maternal organism of fœtuses which are too far developed to be resorbed, and for the continuation of whose normal development the mother has insufficient vitamin E.

In other instances the mother may have sufficient vitamin E to produce her litter, but gestation may be prolonged from the normal 21½ days up to as many as 32 days (Barrie, 1938*a*). Such large increases in the gestation period are rare, but animals judged to be suffering from slight vitamin-E deficiency often have a gestation period two or three days longer than the normal. I have no explanation to offer for this phenomenon, but it does seem likely that it is in some way connected with the function of the corpus luteum.

Let us suppose that an animal receives sufficient vitamin E on mating to carry her pregnancy to term and deliver a normal litter, then in many cases it will be found that her stock of vitamin E is exhausted and her milk does not contain it ; this results in the young showing definite signs of abnormality when they are approximately 18 days old (Evans), (Barrie, 1937). Their fur is soft and cottony, they become extremely

weak and drag their limbs. This abnormality can be cured by the administration of vitamin E (Barrie, 1938*b*). The young are born normal, and this can be shown by exchanging the litter with that of a normal stock animal at birth. If this is done, then it is found that the normal stock young reared by the E-deficient mother become abnormal, whereas the young of the E-deficient rat reared by the stock mother develop normally. The effect is therefore due entirely to deficiency of vitamin E in the milk of the E-deficient mother (Barrie, 1938*c*).

Another striking effect of vitamin-E deficiency, but in this case associated with complete deficiency, is the production of muscular pigmentation and degeneration which was first noticed by Martin and Moore (1936, 1938), Barrie (1938*d*). This pigmentation is particularly noticeable in the uterus, and I have found that it does not respond to massive doses of vitamin E unless the animal is allowed to become pregnant, in which case the pigment disappears, due possibly to the increased circulation in the uterine muscle. As far as can be determined, the pigmentation has no ill-effects on gestation, as animals in which the uterus was very darkly coloured have been successfully mated and have delivered living young after receiving a dose of vitamin E. If, as is occasionally the case, fibroids are present in addition to pigmentation, then pregnancy does not as a rule take place. In an experiment on 35 animals, shortly to be published in detail, I have found that pregnancy following massive dosage with vitamin E is capable of curing this uterine pigmentation. Laparotomy was performed on a vitamin-E-deficient animal with full aseptic precautions: the uterus was found to be very darkly coloured and a small portion was removed to serve as a colour control. The animal was given massive doses of vitamin E and then operated on again three weeks later. There was no change in the colour of the uterus. The animal recovered from the second operation and after seven weeks, during which dosage with vitamin E was continued, it was killed and the uterus preserved. There was no alteration from the original dark colour. In another rat the uterus was found to be discoloured at the first operation and, as in the case of the first animal, there was no improvement following dosing. After recovery from the second operation this animal was mated and delivered and reared a normal litter of two young. When the litter had been weaned, the mother was killed and the uterus was found to be normal in colour. The increased uterine circulation associated with pregnancy was probably adequate to remove the pigment in the blood-stream.[1]

It may seem that vitamin-E deficiency has been claimed to have too many effects, but one would expect many effects if, as there is good reason to believe, vitamin E plays an important rôle in connexion with the normal function of the anterior lobe of the pituitary gland, the secretions of which are known to produce such diverse effects. A rat suffering from vitamin-E deficiency is very like a hypophysectomized animal. It has the same characteristic soft white fur; the deficiency of lactation, the disturbances of pregnancy, the thyroid deficiency, can all be explained on the basis of anterior pituitary involvement, and added to these is the histological evidence of degranulation in the cells of the anterior lobe.

It is not within my province to deal with the clinical applications of vitamin E, but I should like to point out that in addition to its now accepted use in the treatment of habitual abortion, it may well prove to have value in cases of deficient lactation and in the prevention of some types of toxæmia. The work of Shute in Canada suggests very strongly that this is the case.

The occurrence of vitamin E in the normal diet is very low, and when one considers the instability of the vitamin, it seems highly probable that a partial deficiency in the human subject frequently occurs.

[1] Museum jars were shown illustrating this experiment.

REFERENCES

BARRIE, M. M. O. (1937), *Lancet* (ii), 251.
Id. (1938*a*), *Biochem. J.*, **32**, 1467.
Id. (1938*b*), *Nature*, **142**, 799.
Id. (1938*c*), *Biochem. J.*, **32**, 1374.
Id. (1938*d*), *ibid.*, 32, 2134.
Id. (1939), *J. Obst. & Gynæc. Brit. Emp.*, **46**, 49.
EVANS, H. M. (1928), *J. Biol. Chem.*, **76**, 273.
MARTIN, A. J. P., and MOORE, T. (1936), *Chem. Ind.*, **55**, 236.
Id. (1938), *ibid.*, **57**, 973.
SHUTE, E. (1937), *Surg. Gynec. & Obst.*, **65**, 480.
Id. (1938), *Am. J. Obst. & Gynec.*, **35**, 609.

Professor F. J. Browne : *A criticism of current views on the value of vitamin E in habitual abortion.*—Considering the clear-cut results of vitamin-E deficiency in rats it was inevitable that vitamin-E preparations should be used in cases of human abortion. Results have been reported by, amongst others, Vogt-Möller (1933), Watson and Tew (1936), Currie (1937), and Shute (1938). Taking all these reports together it is apparent that the use of wheat germ oil in habitual abortion is followed by success in about 75 to 80% of cases. At first sight this appears convincing. It is, however, disconcerting to find that equally good or better results have been obtained by other methods of treatment. Thus it is well known that good results follow the use of progestin. I have collected from reports in the literature 89 cases treated by this substance with 86% success. I am aware that there may be some connexion between vitamin-E deficiency and insufficiency of the corpus luteum for Rowlands and Singer have shown that the anterior pituitary gland of rats fed on a diet deficient in vitamin E contains less prolan A and B than normal, and this might conceivably explain the comparable results of administering vitamin E and progestin in cases of habitual abortion. Ley (1937) reported on the use of vitamin C in habitual abortion. He gives sufficient by the mouth to secure a daily excretion of 200–300 mgm. in the urine. Ten women were thus treated, all of whom had had at least two previous abortions, and all produced living children at term. Sellheim in 1933 reported a series of eight cases of habitual abortion treated by injecting pregnancy serum—10 c.c. every fourteen days, and of the eight cases seven were successful. Apparently it does not matter at what time in pregnancy the serum is taken. Rosenfeld (1938) treated 20 patients in a similar way but used 5 c.c. once weekly, and 19 of the 20 gave birth to normal living infants. Finally Reuter (1937) reported good results from the use of cold baths alone. It is relevant to note that Shute considers the usual dose of wheat germ oil, viz. 3 to 5 minims daily with which others have obtained successes, to be useless, and that enough must be given to reduce the œstrin-like antiproteolytic substance in the serum to normal. He gives 12 to 24 drams in the first twenty-four hours, and 1 dram daily thereafter.

It seems, therefore, that a moderate and fairly uniform degree of success follows the use of a large variety of therapeutic measures in idiopathic habitual abortion, and it is not surprising if doubts are beginning to arise in the minds of some of us regarding the real value of any of them. Malpas has shown that the abortion rate in any given population is about 18%, and of these 18 he calculates that 17 abort from a casual or random cause such as trauma or infection, and one from a recurrent cause. He also finds that the spontaneous cure rate, i.e. the likelihood of the next pregnancy continuing to term without any treatment, is 78·4% after one abortion ; after two successive abortions it is 62%, and after even three successive abortions it is 27%. These facts must be taken into consideration in assessing the value of any therapeutic measure. The question could be settled even more definitely if alternate cases were

treated as controls, and this has been done during the last year or two at University College Hospital. To Dr. Muriel Boycott, who looks after these cases, I am indebted for the following figures, which give the results up to the present time: 18 cases of habitual abortion have been treated, all being patients who had at least two and most of them three spontaneous abortions, and none having had a living child. Of the 18 cases eight were treated by progestin and three by vitamin E—all successful; seven were controls and received no treatment. Of the seven controls, two were hospitalized, and five were treated as out-patients. All seven controls were successful and gave birth to living children at term. In conclusion I shall quote Wilbur, who writes as follows: "The necessity of vitamin E for normal embryonic growth in animals other than the rat and the mouse has not been established. . . . It is difficult to obtain proof that vitamin E is of value in treatment of . . . habitual abortion in human beings." With this statement I do not see any reason to disagree.

REFERENCES.

CURRIE, D. (1937), *Brit. M. J.* (ii), 1218.
LEY, L. (1937), *Munchen. med. Wchnschr.*, **84**, 1814.
MALPAS, PERCY (1938), *J. Obst. & Gynæc. Brit. Emp.*, **45**, 932.
REUTER (1937), *Fortschr. d. Med.*, **55**, 201.
ROSENFELD, S. S. (1938), *New York State J. Med.*, **38**, 440.
ROWLANDS, I. W., and SINGER, E. (1936), *J. Physiol.*, **86**, 323.
SELLHEIM, H. (1933), *Zentralbl. f. Gynak.*, **57**, 2226.
SHUTE, E. (1938), *Am. J. Obst. & Gynec.*, **35**, 249.
VOGT-MÖLLER, P. (1933), *Acta obst. et gynec. Scandinav.*, **13**, 219.
WATSON, E. M., and TEW, W. P. (1936), *Am. J. Obst. & Gynec.*, **31**, 352.
WILBUR, D. Z. (1938), *Arch. Int. Med.*, **61**, 323.

Section of Neurology

President—J. G. GREENFIELD, M.D.

[*February* 16, 1939]

Cerebral Aneurysm with Papillœdema.—E. A. CARMICHAEL, M.B.

M. H., widow, aged 41.

21.5.37 : First admitted to the National Hospital.

Left-sided headaches eight years. Continuous for several months. Still worse last three weeks.

Family history and previous history.—Not relevant.

History of present condition.—Onset of headache was in last month of pregnancy. Severe fronto-vertical pain, a continuous aching. Continued for one month after delivery, then ceased. From then until her first admission she had intermittent bouts of severe headache lasting one week. Amenorrhœa six years before admission for nine months. Headaches ceased during this time. One year later—fainting attacks —? fits. Unconscious for periods from two minutes to two hours. Had bitten her tongue.

On examination.—No definite neurological signs except absent ankle-jerks. Blood-pressure 185/115. Cerebrospinal fluid : Slightly yellow ; cells : 1 per c.mm. ; total protein : 0·15 grm.%. Reactions : Nonne-Apelt + ; Pandy +. Lange 0112332110. Wassermann : Negative.

Radiography showed an area of fairly extensive calcification on the left side above and to the left of pituitary area.

Following discharge from hospital headaches increased. Worse lying down. Not aggravated by coughing or sneezing.

11.2.38 : Second admission.

On examination.—No new physical signs except : Blood-pressure 150/105. Visual fields showed a right homonymous defect in the upper quadrants.

Cerebrospinal fluid : Faintly yellow ; cells : 1 per c.mm. ; total protein : 0·12 grm.%. ; Nonne-Apelt and Pandy reactions positive. Lange 0001222100.

Radiography : Calcification as before. Some erosion of sphenoid ridge on left. Optic foramina normal.

Arteriogram (thorotrast) : A large aneurysm of left internal carotid pushing middle cerebral artery backwards. It was distal to the posterior communicating branch.

Three days later onset of right hemiplegia affecting mainly upper limb ; doubtful slight motor aphasia ; misty vision in both eyes.

Ophthalmoscopy : Right : Appearance suggestive of old hæmorrhage which had absorbed to nasal side of disc. Left : Disc margin somewhat blurred nasally, with hæmorrhage at first branch of superior temporal vein.

Patient made a good recovery from the hemiplegia.

On readmission (17.10.38) she had been free from severe headaches, but complained of failing sight. Only occasional slight generalized headaches on waking. No vomiting.

On examination.—Visual acuity : R. $\frac{6}{6}$. L. $\frac{6}{9}$. Fields : Right homonymous quadrantic defect a little increased. Fundi : R. disc reddened with indefinite margins. Veins engorged. Similar appearance on the left. No recent hæmorrhages. No exudate. Swelling about 2D. Appearance of early papillœdema.

Slight residual right hemiplegia. No aphasia. Plantars flexor. Slight cortical sensory loss in right hand. Blood-pressure: 195/120. Cerebrospinal fluid: Initial pressure 300 +. Faintly straw-coloured. Cells: 1 per c.mm. Total protein: 0·10 grm.%. Nonne-Apelt and Pandy reactions positive: Lange 0011122100. Blood urea 17·6 mgm.%.

Jaw-winking Syndrome.—P. H. SANDIFER, M.D. (for J. ST. C. ELKINGTON, M.D.).

The patient, W. H., aged 9 years, comes of a healthy family in which no similar trouble has been observed. From early infancy it was noticed that the left eyelid moved up and down synchronously with the movements of the jaw. This condition has persisted and is associated with ptosis of the left eyelid. The movements occur when the jaw is open and shut with the mouth empty, but are more marked when he is eating, and especially when the mouth is full. The right eye is normal and no similar movements are observed in the palate or pharynx. No other abnormal signs are present on examination.

Discussion.—Dr. MACDONALD CRITCHLEY asked whether the raising of the eyelid took place when passive movements of the mandible were made.

Dr. SANDIFER demonstrated that it did.

Subclinoid Aneurysm.—G. C. KNIGHT, F.R.C.S.

E. S., female, aged 69.

History of present condition.—While in her bath, two and a half years ago, patient suddenly developed severe pain at base of spine, quickly spreading to back of neck and round right eye and forehead. Not unconscious. Since then, has had almost constant pain over right eye and face. Three days later, ptosis of right upper eyelid. Four weeks later, she vomited twice and occipital pain developed.

Arteriography 28.4.38: Subclinoid aneurysm of right internal carotid. Right internal carotid was digitally compressed. A left hemiplegia occurred after twenty minutes' compression. It was therefore not ligated. Hemiplegia promptly recovered when the compression was relieved.

Since then pain in the eye has become worse.

On examination.—Pupils: Small, right larger than left. No reaction to light, right eye. Both optic discs arteriosclerotic. Ocular muscles: Ptosis of right lid. Patient can raise upper lid. Right levator acting. Right external rectus and internal recti acting. Right superior oblique: Some action. Right inferior rectus, acting, through 3°. Superior rectus and inferior oblique paralysed. Convergence: Absent. Cornea not now anæsthetic. Severe pain in 1st and 2nd divisions of right 5th nerve.

Heart enlarged. Blood-pressure 270/120. Blood-vessels thickened.

6.12.38: Right common carotid compressed digitally for twenty minutes subcutaneously. Pain in head relieved during this time. Hemiplegia did not develop.

Operation, 9.12.38 (local anæsthetic).—Right common carotid exposed and ligatured. Pulsation was re-established in internal carotid after eight to ten minutes by collateral circulation from the opposite side. Wound closed.

Pain completely relieved by operation and (6.1.39) has never returned.

Discussion.—Mr. KNIGHT, in reply to Dr. Carmichael, who asked whether he advised the tying of the common carotid in cases of aneurysm, said that at one time he thought it was rather dangerous because of the risk of an embolism being produced by the collateral circulation, and he had therefore preferred ligation of the internal carotid. But Mr. Jefferson's experience in Manchester had shown that ligation of the common carotid was not more dangerous—possibly less dangerous—than ligation of the internal. This case had shown that the collateral circulation via the external carotid could sometimes be turned to useful account in preventing a hemiplegia, in those cases where the risk of this complication contra-indicated ligation of the internal vessel. In reply to a further question he said that the patient had had certain objective sensory loss, but this had disappeared since the operation.

Mr. GEOFFREY JEFFERSON said that the idea was put forward, in Germany particularly, that if the common carotid were tied there was a greater risk of embolism than if one tied the internal. The idea was that one had a thrombus at the site of the tying of the ligature, and the returning blood from the external carotid might sweep off a clot and carry it into the internal carotid. One of his assistants had been making a survey of cases from the point of view of ligature of the carotid for aneurysms only. The earlier literature was entirely unreliable. Although on the whole perhaps the tying of the common carotid was a poor operation as compared with the tying of the internal, it should at least reduce the risks of rupture, and so far, in the series in which a ligature of the common carotid—or in some cases of the internal—had been made no patient had as yet died of rupture, although he was fully aware that that might occur. Referring to the first case shown at that meeting by Dr. Carmichael, it was well to remember that no aneurysm had ever calcified over the whole of its circumference ; there was always a weak point where the aneurysm joined the main trunk, and it was at that point that it was most likely to leak if it occurred at all. Up to a point calcification was a sign of stability. In a case with an aneurysm of the size shown by Dr. Carmichael one would expect the patient to have papillœdema. In the analysis he published a year ago a number of the cases with papillœdema were included, though most had optic atrophy. There were few aneurysms of the size observed by Dr. Carmichael.

In reply to the President, who asked what was the relative efficacy of tying the internal and of tying the common carotid in aneurysms, Mr. Jefferson said that perhaps in a few months' time he might be able to answer that question because the whole matter was at present being surveyed. He did not think embolism occurred ; what did happen was that the blood supply was cut down with subsequent thrombosis.

Myopathic Weakness of Quadriceps.—D. DENNY-BROWN, M.B.

L. W., female, aged 42, attended the Neurological Clinic of St. Bartholomew's Hospital complaining of a weakness of the lower limbs of very gradual onset and progressive increase of severity over a period of five years. There is a family history of tremor of the hands, from which she also suffers. Her husband has had a specific infection which was early and adequately treated. The patient's blood Wassermann reaction has been consistently negative.

She noticed the weakness in the lower limbs by falling down when attempting to hurry. This was especially liable to happen when she was descending stairs, but gradually she had more difficulty in walking up steps. The weakness was more obvious if she were distressed or excited, and she was then more liable to fall, but she had not fallen as a direct consequence of emotion. Very gradually she had lost ability to run or move quickly without her knees collapsing.

On examination.—Rapid fine tremor of both hands, but no weakness or wasting in upper limbs. Cranial nerves normal. Moderately severe weakness of extension of both knees ; quadriceps muscles on both sides wasted, especially vastus internus. All other movements of the lower limbs were of full power, and no other wasting was found. The shoulder and pelvic girdle musculature was unaffected, and there was no impairment of stability of the trunk in walking. There was no sensory loss, and no fibrillation. The tendon-jerks were brisk and equal except that the right knee-jerk was absent and the left reduced to a slight flicker in the wasted vastus internus. Plantar responses flexor.

It is thought that the condition is that described by Bramwell in *Proc. Roy. Soc. Med.*, 1922, **16** (Neur. Sect., 1), under the title "Symmetrical Atrophic Paresis of the Quadriceps Muscle of Probable Myopathic Origin". The onset is much earlier than in the cases described by Bramwell (53 and 59), and in two other cases personally observed.

The patient has been having glycine, 5 grm. twice daily, since June 1938, with considerable improvement, both in increased ability to mount stairs and in increased bulk of the quadriceps muscles. The knee-jerks are as when first observed. She still has great difficulty in walking downstairs.

Discussion.—Dr. ANTHONY FEILING said that the peculiar distribution of the wasting in this case recalled the appearance seen in the thighs in cases of peroneal muscular atrophy when well-marked signs were present—foot drop, and so on. Was it possible that this might be an atypical case of peroneal atrophy where the wasting began in the thighs in this peculiar manner?

Dr. C. P. SYMONDS believed this was a true example of the condition described by Bramwell. The unusual feature was the age of the present patient. These patients did represent a definite group. There were rare cases in which the wasting and weakness of the quadriceps, however long the condition persisted, remained limited to that region, with no fibrillary twitching and only slight disability. He agreed with Dr. Denny-Brown that the muscular atrophy associated with hyperthyroidism was not so limited. In the cases he had seen it had been present and obvious in the upper before becoming evident in the lower limbs. One hesitated to generalize from a limited experience. The thyrotoxic cases were rare, but in those he had seen or read about the atrophy had been fairly widespread in the upper limbs at an earlier stage. Whilst agreeing with Dr. Feiling on the resemblance of the muscular atrophy so far as the thighs themselves were concerned, he did not accept his suggestion that this might be an atypical case of muscular atrophy, because he believed that in that disease the wasting ascended from the feet upwards. Others than neurologists were very apt to regard these elderly people as suffering from hysteria. The patients might still preserve their knee-jerks at a time when they had considerable disability. It was rather an accident of the localization of the atrophy that they lost their knee-jerks. They had considerable difficulty in walking over rough ground and getting upstairs.

In reply to the President, who asked if there was any evidence that this condition was myopathic, Dr. Symonds said that he did not know whether Bramwell had any observations on that point. He had not persuaded his own patients to allow any biopsies to be done.

Dr. DENNY-BROWN said that he, too, did not know of any biopsy.

POSTSCRIPT (D. D.-B., 1.5.39).—The patient has since submitted to further investigation which hitherto she had refused. Cerebrospinal fluid normal. Wassermann negative. Biopsy: Right vastus externus muscle shows myopathic changes of the type

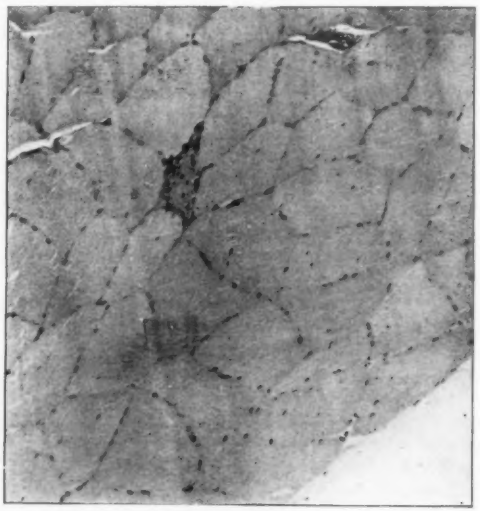


FIG. 1.

recorded by Nevin in a study of senile myopathy of more widespread distribution (*Quart. Journ. Medicine*, 1936, **29**, 51). There are small necrotic muscle-fibres scattered throughout the muscle. These show a great increase of nuclei, and the sarcoplasm

stains deeply with eosin (fig. 1). In longitudinal section the necrotic change extends throughout the length of the fibre. In places small fibres in a more advanced stage are represented by bands of nuclei. The remaining muscle-fibres are larger than normal, and the majority show nuclei in the substance of the fibre, instead of the normal arrangement around the periphery. There is no inflammatory reaction.

Communicating Hydrocephalus simulating Cerebral Tumour.—C. WORSTER-DROUGHT, M.D., and G. C. KNIGHT, F.R.C.S.

P. C., aged 12 years. Admitted to West End Hospital for Diseases of the Nervous System, on 5.12.38.

History of present condition.—Four weeks ago developed a severe headache with nausea and vomiting. Diplopia for two weeks. Headache became less and vomiting ceased.

Past history.—Scarlet fever when aged 5 years.

Physical examination.—Diplopia for past two weeks. Right superior oblique paresis. Nystagmus present to right and left. Papillœdema: Right: + 1·5 D. Left: + 3 D. Hæmorrhages present around both discs. Slight intention tremor on finger-nose test.

Cerebrospinal fluid (6.12.38): Naked eye, clear and colourless. Cells, none. Total protein: 0·025%. Globulin: No excess. Wassermann and M.K. reactions negative. Lange 0011000000.

Blood Wassermann and M.K. reactions negative.

Ventriculography, 8.12.38 (G. C. Knight).—Under local anæsthetic 76 c.c. air injected showed gross internal hydrocephalus, including fourth ventricle.

Operation, 12.12.38 (C. P. G. Wakeley and G. C. Knight).—Suboccipital decompression. Transverse incision. Posterior arch of atlas exposed. Needle inserted in the previous ventricular opening led to escape of air under pressure. Occipital bone removed widely on both sides, the dura was opened, and the sinus secured between silver clips. Considerable downward displacement of the cerebellar tonsils forming a pressure cone with impaction was noticed. There was no widening of the vermis, enlargement of the cerebellar hemispheres, or broadening of the cerebellar tonsil, to indicate possible tumour. Both cerebellar hemispheres were tapped and the vermis incised. The fourth ventricle was opened and appeared dilated at this point, suggesting an obstruction at a lower level, possibly due to numerous though slight adhesions which were found between the dura and cerebellar surface.

15.12.38: Still complains of headache and has vomited on three occasions. Temperature and pulse normal.

21.12.38: Cerebrospinal fluid removed by lumbar puncture. Examination (Dr. W. E. Carnegie Dickson) showed moderately turbid fluid, giving centrifugalized deposit of compact reddish-brown red blood-cells, &c. Supernatant fluid remained brownish-red in colour, due to mixture of both fresh and partially hæmolysed R.B.C. The films showed that the cells probably amounted to many hundred per c.mm. Varieties of cell (200 counted): Polys. 43·5%; small lymphos. 42·5%; small endos. 10·0%; large endos. (monos.) 4·0%. In both: Total protein 0·5% approximately. The cell count was made on those cells which were still identifiable, but there were also numerous "ghosts" too degenerated for identification. A few hæmatoidin crystals also found. The condition is evidently one of hæmorrhage, and no bacteria were detected in Leishman, Gram, and Ziehl-Neelsen films of the centrifugalized deposit.

Culture: No growth in any of the twelve tubes inoculated. Films, 22.12.38: Examined from all 12 cultures, and *no* micro-organisms of any kind found on forty-eight hours' incubation.

Commentary.—When first seen, considering the headache, vomiting, papillœdema and nystagmus, the diagnosis certainly appeared to be one of subtentorial neoplasm, especially as within a week the papillœdema increased from 1 dioptre in

each eye to 1·5 D in the left and 3 D in the right. The boy became rapidly worse and consequently operation was carried out. For the first few weeks, owing to increasing bulging, it was necessary to tap the hydrocephalus through the decompression opening. The hernia was evidently pure meningocele and not due to increased dilatation of the ventricles. He was then started on deep X-ray applications directed to the choroid plexuses in order to reduce their activity, with the result that he has steadily improved and no further tapping has been necessary for the past three weeks. He is now free from symptoms such as headache and vomiting, and the papillœdema has disappeared.

There is nothing in the history or in the results of investigation to suggest meningitis. The boy was under observation by a local practitioner (Dr. Apergis) from the day he was taken ill, and it is understood that there was no pyrexia or suggestion of meningitic signs. Further, the cerebrospinal fluid removed within a week of the onset of the illness does not suggest remitting meningitis, and the condition indicates a communicating hydrocephalus rather than a closed one. Inquiry failed to show any history of head injury that might be responsible for a traumatic arachnoiditis. Thrombosis of the superior longitudinal sinus has been considered although there is no toxic factor to suggest this, and one would also expect some signs in the legs of upper motor neurone involvement, such as extensor plantar reflexes, as the result of accompanying œdema (leg areas) on each side of the great longitudinal fissure.

Discussion.—Mr. G. C. KNIGHT said that at operation the only cause for the obstruction which could be found were numerous light adhesions all over the surface of the cerebellum, but he could not say definitely that these were causative as similar adhesions were often seen in cases of raised intracranial tension. About three weeks after the operation the decompression area became extremely tense ; and on tapping it was found that the mass in this area was not brain substance but fluid collected externally to the cerebellum. That had been removed on several occasions, and now it was not necessary to tap it, because treatment by deep X-rays was diminishing the action of the choroid plexus.

In reply to the President, Dr. Worster-Drought said that there were no unfavourable sequelæ to operation.

Dr. STANLEY BARNES thought that this might possibly be one of those relatively rare cases in which an attack of meningitis cleared up but left behind a blocking of foramina causing hydrocephalus. Some years ago he had a case in which symptoms of a similar character were present, and which lived for twelve months after the first signs. On post-mortem investigation it was found that the cause of the hydrocephalus was a tuberculous meningitis which was quiescent. It must be very rare to see any case of tubercular meningitis which did not progress to death within a few weeks, and in which a secondary hydrocephalus was the ultimate cause of death. Although this case might be meningococcal in origin, it is more probable that the inflammation was due to some unrecognized organism or virus.

It was difficult to believe that excessive secretion by the choroid plexus could be the real cause of the hydrocephalus. There was much clinical evidence that the absorptive apparatus (Pacchionian bodies, &c.) were capable of dealing with any quantity of fluid which the choroid plexuses were able to secrete, and in addition a certain amount got away through the foramen magnum along the posterior roots of the cord. Evidence on this latter point was confirmed by those cases in which a malignant growth, having burst into the central canal, gave rise to secondary growths in the region of the posterior root ganglia of the cord. The finding of these tumours in that position proved that at least some of the cerebrospinal fluid was filtering away along the posterior rootlets in the spinal cord region.

Mr. GEOFFREY JEFFERSON said that such a case of obstructive hydrocephalus due to fibrosis of a meningitis presented a very difficult problem for surgery. One difficulty was to know exactly where the obstruction was. Was it just in the cisterna ambiens ? That was a very important point. If they were to open the 3rd ventricle and operate behind the chiasma, it presupposed that once the fluid got into the top end of the cisterna pontis, it would find its exit. That could happen, he thought, but he did not know that such a success could be counted on, and an alternative method one had to consider was the removal of the choroid plexuses. He supposed that

the case shown was doing fairly well, and he was not suggesting that this last procedure should be followed in this case. But if something had to be done then he would coagulate the choroid plexuses, which was quite a small operation and could be done through a small opening. He believed that it would be worth while.

In reply to the President, Mr. Jefferson said that he considered that even if this case were accepted as a communicating hydrocephalus he would consider the procedure worth doing.

Dr. C. P. SYMONDS, speaking in answer to a question, as to whether this case could be said to fall into the group which was attributed to thrombosis in the superior sagittal sinus as in one of the forms of so-called otitic hydrocephalus, said that he thought it unlikely that it came into that group. There was no evidence of infection in the preliminary story. Thrombosis in the sagittal sinus, if non-suppurative, might be an extraordinarily quiet affair, without very much evidence of constitutional illness. But in the present state of knowledge, or ignorance, it was unsafe to pursue the idea, in the absence of a history of infection, that the case belonged to that group. There was another point which he considered told against putting the case in such a category. From America he gathered that in cases in which ventriculography had been performed the ventricular system was shown to be very little distended. It presented a symmetrical picture with little or no distension of the ventricles, and the distension of the whole ventricular system in this case right down to and including the 4th ventricle would suggest an obstructive cause low down.

He could recall a case which occurred in a schoolboy, the symptoms coming on suddenly after a cold. In that case he, as Dr. Worster-Drought had done, gave a confident diagnosis of cerebellar tumour, but the parents, because the boy was so well, would not have anything done for a long time. As the symptoms continued, however, an operation was carried out six months later by Mr. Hugh Cairns and a number of adhesions were found. The ventriculogram showed a distension of the 4th ventricle, and they did not quite know what they were going to find, although the boy had none of the symptoms one usually associated with tumours in that situation. He wondered whether Dr. Worster-Drought had inquired in this case as to the possibility of head injury either recent or remote. In a paper published last year four cases were published with post-mortem evidence of internal hydrocephalus following head injury after a latent interval, and proved to be due to a meningitis obstructing the outflow from the 4th ventricle, presumably traumatic.

Dr. WORSTER-DROUGHT replied that in the first place meningitis was very carefully considered and ruled out for the reason that the case was under observation by his local doctor from almost the first day of illness and he found nothing to suggest meningitis. Again, the hydrocephalus appeared to be of a communicating rather than of a closed type; in other words, there was no real evidence of foramina block. He was grateful for Mr. Jefferson's suggestion, but at present the case appeared to be improving satisfactorily although it might be necessary to coagulate the choroid plexus at a later date if the condition recurred. Careful inquiry had been made as to injury on account of the possibility of a traumatic arachnoiditis at the base of the brain or in the cervical region, but no history suggesting even a mild injury was forthcoming.

Calvé's Disease (Osteochondritis Juvenilis).—MACDONALD CRITCHLEY, M.D.

Male, aged 47. A year ago continuous pain developed over front of left thigh, worse when recumbent, on coughing, sneezing, and straining. At the same time aching across sacrum occurred, at first continuous but for last three months only on coughing and sneezing. Four months ago left leg began to weaken. On walking left ankle would often give way, the foot inverting. Later dorsiflexion of left ankle became difficult. Later still left leg dragged. Two months ago he noticed left leg was getting thinner than the right.

Past history.—Denies any accidents or injuries. Never had any trouble connected with legs or back.

Family history.—No neurological or orthopædic condition.

On examination.—Weight on admission 7 st. 2 lb. Average 8 st. 5 lb. (Present weight 7 st. 12 lb.) Range of movement of spine much reduced in all directions. Moderate degree of kyphosis and lumbar lordosis. Local pain felt on percussing D. 10–L. 1 as on coughing and sneezing. Tendon-jerks normal in arms. Both

knee-jerks absent. Right ankle-jerk absent and left just obtainable. Abdominal reflexes present but less brisk left than right. Right plantar response variable but left always extensor. Power reduced in left leg, maximal distally with some distal loss on right. Wasting of left thigh and leg, maximal below knee where tibia forms a sharp edge. On walking he limps on the left leg and has to pick up left foot higher than right to allow for foot-drop.

Investigations.—Cerebrospinal fluid: Initial pressure 130 mm. On bilateral jugular compression, 300 mm.; on release, 180 mm. On removing 6 c.c., 20 mm. Rapid rise and fall. Fluid yellow with clot formation. No cells seen. Protein 2·1 grm.%. Nonne-Apelt and Pandy +++.

Lange 0000122222. Wassermann reaction negative.

Blood Wassermann reaction negative.

Radiographs.—Chest: Normal. Spine: Collapse of the bodies of D. 9 and 11.

The nature of this vertebral deformity is not altogether clear. The two diagnoses most favoured are Calvé's disease and a congenital deformity of the 9th, 10th, and 11th dorsal vertebræ. Whether the neurological symptoms are directly referable to his vertebral deformity is another point of uncertainty.

Discussion.—Dr. F. PARKES WEBER took exception to the name "Calvé's disease". Calvé and Perthes separately described and worked out the juvenile (so-called) "osteochondritis" of the hip-joint, the breaking-up of the epiphysis of the head of the femur. The analogous condition in the vertebral bodies should be called Scheuermann's disease, after H. Scheuermann, the Danish orthopædist of Copenhagen (*Zeitschr. f. Orthop. Chirurgie*, 1921, **41**, 305), who maintained that juvenile kyphosis, which had been wrongly attributed to muscular weakness, was really due to a disturbance of the epiphyses of the vertebral bodies (or perhaps one should say "apophyses"), analogous to the epiphyseal disturbance at the hip-joint. As the condition described by Calvé and Perthes was named "osteochondritis juvenilis coxæ", Scheuermann suggested the term "osteochondritis juvenilis dorsi" for the analogous condition in the bodies of the vertebræ.

Dr. PURDON MARTIN asked whether the possibilities of Recklinghausen's disease had been considered, and whether Dr. Critchley could make any other suggestions to explain the high protein of the cerebrospinal fluid.

Dr. ANTHONY FEILING asked whether paraplegia was known to be a recognised complication of osteochondritis juvenilis of the spine.

The PRESIDENT said that he supposed it was possible that the nipping of the veins in the intervertebral foramina might increase the protein.

Epilepsy Treated with Sodium Diphenyl-Hydantoinate. — DENIS WILLIAMS, M.D.

2.12.38: E. W., a married woman aged 33, attended Dr. J. St. C. Elkington's out-patient department at the National Hospital complaining of fits which had occurred every night but one since birth.

Personal history.—No other serious illnesses and no severe injuries. Infancy otherwise normal. Started school when 5 years of age and left at 14, having been in the top class for three years. Passed an examination at the Royal College of Music, and subsequently taught the piano there. Married five years.

Family history.—Father diabetic; mother died of rheumatic fever; two normal brothers. Husband normal. One son, aged 6 months, has a double hare-lip and cleft palate. No deaths or miscarriages. No history of epilepsy, migraine, or mental disease in the family.

Course.—She had convulsions at birth, and continued to have fits every night throughout childhood, of minor and major types. The minor fits were usually nocturnal and rarely less than 10 a night. She woke with an indescribable feeling of something passing over her head, and then for a few moments was unable to respond to what was said, although she was aware of what was taking place. During this time her lips became blue, her face expressionless, and she often micturated. In the day she fell to the ground. She was quite well afterwards. The major fits were always

nocturnal, and consisted in an aura of extreme hunger, extension and raising of the left arm, and then a generalized convulsion, with tongue-biting and incontinence. There was a severe bifrontal headache afterwards. When 5 years old she had a desk to herself at school because of frequent attacks with incontinence. When 10 she was having 10–15 minor fits a night, and occasional diurnal attacks. At the age of 11 menstruation began and the fits became worse. She had major fits for three nights before menstruation, and at least 10 in the intermenstrual period. The attacks became more frequent and severe, and when she was 20 she counted 200 minor attacks in a week.

There were no spontaneous or therapeutic remissions, but she found that each time that she went into hospital the frequency dropped, but returned to its former rate after discharge.

When 29 years old she married, and the fits became worse. The major attacks averaged five a week, and the minor fits interrupted her sleep from midnight onwards. The only night in her life when she was quite free from fits was after her first sexual intercourse. When 32 years old she became pregnant, and the fits became much worse. After a normal labour at full term (August 23, 1938) she did not improve, but was having four major attacks a night. Her husband attended to her continuously after midnight. Her state was unchanged when she attended hospital.

Treatment.—She had been investigated in many London hospitals and had taken anticonvulsants without interruption since childhood. Remedies used: Bromides, in various mixtures up to two tablespoonfuls four times a day; luminal, up to 11 gr. a day; prominal, up to 6 gr. a day; gardinal, 7 gr. a day, as well as less usual therapeutic measures. There was never any remission with a new line of treatment.

On examination.—The facies suggested deterioration, as she had a small head, prognathism, and widely spaced teeth of degenerate shape. The palate was well shaped and there were no other stigmata of degeneration. Intelligence was high, and memory good, and although her movements of expression were slow, careful investigation did not reveal evidence of mental deterioration.

Slight bilateral ptosis, but no other abnormality found in central nervous system. Optic discs normal, pupils equal, central, and circular, reacting well to light and accommodation. Tendon reflexes brisk and equal, abdominals present, and plantar responses flexor. Cardiovascular system normal; blood-pressure 130/85. Blood Wassermann reaction negative; blood-count and urine normal. Skiagram of skull: No abnormality.

Diagnosis: Idiopathic epilepsy.

Present treatment.—The patient was given sodium di-phenyl hydantoinate one capsule (100 mgm.) t.d.s. The fits fell to 1 major and 7 minor in the first month, and she was more alert and active. She then had 1 major fit and up to 12 minor fits for nine consecutive nights at her first menses since pregnancy, and had 7 major attacks during the rest of the month. The dose was increased to 5 capsules a day, 2 at 8 p.m. and 3 at 10.30 p.m.

In the last month she has had two slight minor attacks. She has menstruated and has been upset by moving her home during this time, but says "I feel better than I have ever done since I was born". There have been no toxic effects, and clinical and biochemical investigations show no changes.

Apraxia of the Right Upper Limb with Sensory Changes in the Same Limb and Dysphasia.—P. H. Sandifer, M.D.

Male, aged 68, under the care of Dr. F. M. R. Walshe. Prostatectomy seven months ago. One month later found increasing difficulty in using right hand, which began to feel numb. Only very clumsily could he carry out the movements he intended. These symptoms took five weeks to reach their maximum intensity. Five weeks ago began to have difficulty in speaking. He has become slow to recall proper names. Reading is laborious. Writing is more difficult than before.

On examination.—Dysphasia which is executive as regards spoken speech and both receptive and executive as regards written speech. He can carry out complicated verbal requests. He cannot spell out his name correctly on a typewriter. Calculation grossly impaired. Moderate degree of retinal arteriosclerosis. Left pupil a little bigger than right.

Slight but definite wasting of right intrinsic hand muscles. Power everywhere normal save in right hand where there is some reduction. Apraxia is present in the right upper limb. Thus when combing his hair he slowly and jerkily directs the comb to his face and then, with clumsy sweeping movements, digs the teeth into his nose or cheek. He uses excessive force. The disorder is not due to spatial disorientation as he can place objects (though with mechanical difficulty) in various spatial relationships with other objects. The disorder is more than can be accounted for by incoordination, for simple tests for ataxia are fairly well executed.

Sensation is normal save in the right upper limb. Pin-prick, temperature, and cotton-wool, are not so clearly felt over the dorsum and palm. Vibration sense is diminished below the elbow. Passive movement and joint position sense diminished at right wrist and more so at fingers. Tactile localization is impaired in the hand as is 2-point discrimination. There is astereognosis.

Tendon-jerks exaggerated on right side. Plantar responses flexor.

Heart enlarged to left. Brachial vessels thickened and tortuous. Blood-pressure 175/100. Cerebrospinal fluid : Normal pressure and constituents. Blood Wassermann reaction negative.

An Unusual Case of Sensory Polyneuritis.—DAVID KENDALL, M.B.

20.1.39 : T. L., aged 59, admitted to National Hospital under the care of Dr. Gordon Holmes.

Fourteen weeks before admission he noticed pain and numbness on the right side of the lower jaw. Within a few days the whole of the right side of the face was numb and this rapidly involved the tongue and the left side of the face. Fourteen days later his feet felt numb. The numbness spread from the toes upwards and involved the whole of both limbs in one week from the onset. A few days after appearing in the limbs, the numbness started in the fingers and passed up the arms. Within three weeks of the onset the whole body felt numb. For three weeks before admission he had tingling sensations in his limbs which led to incessant rubbing of his arms with his hands. Throughout his illness he has experienced difficulty in swallowing solids. Food gets lost in his mouth. He cannot keep his false teeth in as he does not know where they are. 2 st. in weight lost in the last five months. 20.11.38 : Admitted to St. Bartholomew's Hospital. While there he received 4 mgm. of vitamin B daily, without any change in his condition.

21.1.39 : Developed retention of urine. 23.1.39 : Became incontinent of urine. 29.1.39 : Bladder function returned to normal.

Past history and family history negative.

Patient has worked as a boiler cleaner for the last thirty-seven years. Uses no special preparations. No other employees have had similar illnesses. Diet not deficient. Moderate alcohol consumption. No history of febrile illness in past year.

On examination.—A very emaciated patient. Speech nasal and slurred. Constant rubbing of hands and arms, even during sleep. Both corneal reflexes absent. Complete failure to appreciate pin-prick over distribution of trigeminal nerves, including the tongue. Gross impairment to perception of light touch, and temperature. Apparent loss of position sense in the tongue. Salivary secretion much diminished. Taste bilaterally impaired. No facial weakness. Slight middle-ear deafness on the right side (of many years' standing). Palate normally elevated on phonation. Palate reflex absent. Pharyngeal reflex just present.

Arms : Wasting corresponding to general emaciation. Marked hypotonia. Power good in all muscle groups. Co-ordination grossly impaired. No fibrillation.

Trunk : Intercostal muscles and abdominal muscles contract well.

Legs: Wasting corresponds to general emaciation. Marked hypotonia. Power good in all muscle groups. Co-ordination grossly impaired.

Reflexes (20.1.39): Biceps present; supinators and triceps equivocal; abdominals absent. Knee and ankle jerks absent. Plantars: Both weak flexor. (23.1.39) All tendon reflexes absent. Plantars not obtained. (1.2.39) Biceps and supinator jerks just obtainable.

Sensation.—Gross impairment of perception of all forms of sensation throughout the body; maximal on peripheral parts of limbs and least marked on neck. Vibration sense just present on clavicles only. No muscle tenderness; superficial nerves not thickened.

Gait grossly ataxic. Patient is only able to walk or stand with support.

Cardiovascular and respiratory systems normal. Abdomen: No abnormality detected. Rectal examination negative.

Investigations at St. Bartholomew's Hospital—

22.11.38: Blood-count normal. 23.11.38: Cerebrospinal fluid clear: four lymphos. per c.mm. Total protein 0·100 grm. %. Lange 0001100000.

At the National Hospital—

24.1.39: Blood-count normal. 26.1.39: Cerebrospinal fluid clear: Cells: 1 per c.mm. Total protein 0·100 grm.%. Nonne-Apelt weakly positive. Pandy positive. Lange 0001221000. Wassermann reaction negative. 3.2.39: Electrical reactions of muscles of face and limbs normal.

A recent finding, since the note was compiled, is that this patient has a considerable quantity of lead in the urine. It is not possible to estimate this accurately because he has become incontinent. His trade has been that of a boiler cleaner, and it has been part of his job to scrape the paint outside boilers.

Discussion.—Dr. GORDON HOLMES said that he could add nothing to the history of this case or its present state, but he was very doubtful with regard to the diagnosis set out by Dr. Kendall. The history was a curious one, beginning with pain and numbness on one side of the face and loss of sensation developing first on that side and within a day or two appearing on the other side of the face as well. The loss of sensation was very profound, but even more striking was the almost total escape of the motor system. The wasting of the arms and legs was only part of the general emaciation, and the motor movements were extraordinarily good in relation to the loss of sensation. As to the question of lead in the urine, when lead affected the nervous system it seemed to fall on the motor rather than on the sensory system.

Dr. D. DENNY-BROWN recalled an unusual case of diphtheritic polyneuritis commencing with numbness in the tip of the tongue and the middle of the lips. The loss of sensation spread, and a few days later affected the tips of the fingers and spread proximally in the limbs. The tendon-jerks were late in disappearing. While he did not think that the present case was one of diphtheritic polyneuritis, he thought it not impossible for the sensory element to be unusually predominant in other forms of polyneuritis.

Dr. C. P. SYMONDS said that he had been extremely interested in this patient. It seemed to him that this kind of case was one which theoretically ought to occur. In other words, if one lived long enough and were lucky one ought to see something of this sort, because it was the corresponding opposite to what after all was not so very rare; the polyneuritis that was exclusively motor was not an extremely rare occurrence. Why should they not occasionally see at the other end of the scale a case that was exclusively sensory? He remembered the case of diphtheritic polyneuritis, certainly not so extensive as this, though it began in the same way; also another case of polyneuritis which was under observation for some time and which was purely sensory and spread all over the body very like Dr. Kendall's case, though not with the same degree of sensory loss. This latter case was apparently due to gold treatment for rheumatoid arthritis. It seemed to him that the increased protein in the cerebrospinal fluid with a normal cell count was in favour of polyneuritis.

Dr. HUGH GARLAND said that it would be interesting to know something about the gastric secretion in this case. He thought that the finding of lead in the urine was of no significance. Lead was found in the urine of many workmen, and had nothing to do with a neurological syndrome.

He had seen four cases of gold polyneuritis, they were all like each other and the motor and sensory disturbances were almost entirely confined to the feet. They were not at all like the case now shown.

Dr. PARKES WEBER asked whether it was worth while giving intensive treatment by intramuscular injections of liver extract. In spite of the blood-count, there remained a bare chance of the symptoms being of the nature of combined degeneration.

Dr. KENDALL replied that as for gastric analysis the patient was too ill to have it done. As to liver extracts the patient had been having large doses of liver for the last four weeks without showing any change. In reply to another question, he said that the electrical reactions of all the muscles were perfectly normal.

Dr. GORDON HOLMES said that the condition was progressive. It was four months since the onset of the case. Since the patient had been transferred from St. Bartholomew's to the National Hospital he had developed sphincter disturbance, with incontinence and retention of urine.

POSTCRIPT (D.K., 30.5.39).—The patient died four weeks later.

Post-mortem findings, described at the meeting on 18.5.39 : Oat-celled carcinoma of the right lung with metastases in the wall of the stomach. The dorsal nerve-roots were grey and, on microscopical examination of the dorsal root ganglia, almost all the ganglion cells had disappeared. The ventral roots were normal. The motor nerve-endings in the muscles showed some early degenerative changes. In addition, chemical analysis of the bones showed the presence of 1·04 mgm. of lead per 100 grm. of bones.

Myopathic Wasting associated with Ptosis and External Ophthalmoplegia.—F. A. ELLIOTT, M.B.

Dorothy K., aged 38. Admitted under the care of Dr. Denis Brinton. For ten years she has had progressive drooping of the lids without relationship to ocular fatigue. For four years, difficulty in turning the eyes in any direction, reading being unaffected. No diplopia admitted. For three years, weakness and wasting of neck, shoulders, and entire upper extremities. No difficulties in relaxing the grasp. Weakness not improved by rest.

Family history.—Negative for myopathy. No cataracts or other stigmata of family decadence.

On examination.—Pupils sluggish to light ; contract on attempted convergence. E.O.M. limited to very slight downward and lateral movement. Bilateral ptosis. Extreme weakness of orbicularis palpebrarum and oris, zygomaticus, and frontalis. Tongue weak but does not deviate. Severe wasting and moderate weakness of sternomastoids, shoulder girdle, and entire upper extremity, except for the relative sparing of upper trapezius, clavicular portion of pectoralis major, rhomboids, and serratus anterior. Supinator longus not conspicuously affected. The trunk, pelvic girdle, and lower extremities appear large, but are normal for age and stature. Collar of tender fat obliterates the tapering from calf to ankle.

Sensation normal. Tendon reflexes brisk. Plantars flexor. No myotonia. No cataract. No reaction of degeneration. Cerebrospinal fluid normal. Blood Wassermann reaction negative.

Dr. PURDON MARTIN said that he had been interested in this case because recently he had had two cases of progressive external ophthalmoplegia with what he regarded as myopathic features. The first, a girl aged about 12, whom he saw at Moorfields with a similar condition in the eyes, had pronounced weakness of nearly all the muscles of the face, but especially the orbicularis oculi. He was rather inclined to think that the case was associated with myasthenia, but the injection of prostigmin did not produce any effect on her, and apart from a weakness of the sternomastoids and the facial musculature, no other somatic muscles were affected. About six months ago he saw a little boy with progressive external ophthalmoplegia, who had a general hypotonia of his somatic musculature. He did not recall having seen any patient in which there was such advanced muscular wasting as in the one shown by Dr. Elliott. Although the condition was usually called progressive nuclear ophthalmoplegia, he thought that quite a good case could be made out for some of these patients being considered as myopathic, and not nervous.

Section of the History of Medicine

President—A. P. Cawadias, O.B.E., M.D.

[*February* 1, 1939]

British Prisoners Released by Napoleon at Jenner's Request

By J. A. Nixon, C.M.G., M.D.

The world-wide eminence of Edward Jenner finds no better illustration than his ability to secure the liberation of British prisoners from countries with which England was at war. It is well known that at Jenner's request Napoleon ordered the release of certain British subjects detained in France when war broke out again after the peace of Amiens. The families and individuals on whose behalf Jenner intervened are the subject of this paper; for some of them were well known and one at least is an interesting medical personality.

Jenner's first attempt was made on behalf of a family called Peploe, who were detained at Paris on their way to Spa. On this occasion he wrote to General Andreossi, whose acquaintance he had made whilst the General was French Ambassador in London. He received no reply but he heard afterwards that the family had been allowed to go to Spa, presumably at his request. (I have been unable to identify the Peploe family.)

His next effort was on behalf of the Earl of Yarmouth. In pursuance of a promise to the Earl's father, the Marquess of Hertford, Jenner addressed an appeal to the National Institute of France in 1803 [1].

"Gentlemen, Pardon my obtruding myself on you at this juncture. The Sciences are never at War. . . . Permit me, then as a public body with whom I am connected to solicit the exertion of your interest in the liberation of Lord Yarmouth."

It is puzzling to discover what happened in the case of Lord Yarmouth. The Dictionary of National Biography describing Lord Henry Seymour, says that he was born in Paris in 1805, his father, then Lord Yarmouth, having been detained in France on landing just after the Treaty of Amiens. Lord Yarmouth was released in 1806 through Fox's intercession with Talleyrand. In Duff-Cooper's *Talleyrand* [2] a fuller account is given of Lord Yarmouth and his activities in Paris at this time.

"Among the Englishmen who had been detained in France as prisoners at the renewal of the War was Lord Yarmouth whose portrait at a later age has been drawn for us by the pen of Thackeray as the Marquess of Steyne and by that of Disraeli as the Marquess of Monmouth. . . .

Lord Yarmouth was selected by Talleyrand as a suitable intermediary between himself and Fox. The British Government however gave Lord Yarmouth a colleague in the person of Lord Lauderdale whom Talleyrand in his Memoirs blames for the failure of the negotiations. . . . Sorel says of Yarmouth, 'he soon began to give evidence of those qualities of a sly and obstinate bulldog which are revealed in all Englishmen as soon as the interests of England are at Stake'. Montrond was set to spy upon him but unfortunately for Montrond, Yarmouth had the stronger head of the two and would drink the Frenchman under the table acquiring the while a great deal more information than he gave. In September 1806 Fox died and with him perished the last hope of peace between England and Napoleon."

In Doyle's *Official Baronage of England* [3] there is a portrait of Lord Yarmouth (as Marquess of Hertford). It is recorded that he was appointed Commissioner and Plenipotentiary to treat with France on June 26, 1806. Mowat [4] says that after being released from Verdun by order of Napoleon he came to Paris and renewed an old acquaintance with Talleyrand. On June 14, 1806, Fox had written a letter to Talleyrand at the end of which is the sentence

" Au surplus Lord Yarmouth a toute ma confiance : tout ce qu'il vous dira, vous pouvez croire que c'est moi même qui vous le dis " [5].

The anonymous author of *A Picture of Verdun* [6] states " at length in June 1806 the Earls of Elgin and Yarmouth received their passports for England and after some few days the latter returned to Paris in a diplomatic character and during his stay there, having need of couriers to carry dispatches to England, he procured the release of several of his friends among the *détenus* and prisoners of war who were suffered to return home as *estafettes*.

The *Dictionary of National Biography* says that he led an epicurean existence in Paris, rarely if ever visiting England. He amassed a splendid collection of pictures and articles of vertu which he left along with his Irish estates to Sir Richard Wallace. On the death of Wallace, his widow, Lady Wallace, gave (or bequeathed) this collection to the nation, whilst Sir Richard during his lifetime founded the British Hertford Hospital in Paris in memory of his kinsman and benefactor, the Marquess of Hertford, Lord Yarmouth of Jenner's letter.

In 1804 one of the most beautiful of the Napoleon series of medals was struck commemorative of the Emperor's estimate of the value of vaccination. It has been said that it was at the same time intended as a mark of personal honour to Jenner by appropriating one side of the medal to his bust . . . the obverse of some of the early vaccination medals was left blank. Subsequently it was occupied by the head of the Emperor.

Early in 1805 Jenner addressed himself directly to Napoleon humbly requesting that two of his friends, both men of science and literature, might return to England. These two men were Mr. William Thomas Williams residing at Nancy ; the other Dr. Wickham, then in Geneva. Napoleon was at that time in Italy but Mr. Williams had an opportunity of delivering a copy of the letter into his Majesty's hands as he passed through Nancy. A duplicate was presented by Baron Corvisart, the Emperor's physician in June 1806. In the following July Corvisart informed Mr. Williams that the Emperor had listened to Jenner's petition and had granted liberty both to himself and Dr. Wickham. Baron [7] adds as a footnote to the Nancy incident,

" It was either on this or some similar occasion, when Napoleon was about to reject the proffered petition, that Josephine uttered the name of Jenner. The Emperor paused for an instant and exclaimed, ' Jenner ! Ah, we can refuse nothing to that man '."

Fosbrooke [8] in his Berkeley Manuscripts (1821) gives a fuller account of this incident.

" When Dr. Wickham was made a prisoner in France our Philosopher (namely Jenner) was applied to as the fittest person for addressing to Buonaparte a petition soliciting that physician's liberation. This was at the time of Napoleon's greatest animosity to this country. It happened thus ; the Emperor was in his carriage and the horses were being changed. The petition was then presented to him (presumably by Mr. Williams at Nancy as previously related). He (Napoleon) exclaimed ' Away, Away ! ' The Empress Josephine who accompanied him said ' But Emperor, do you see who this comes from ? Jenner '. He changed his tone of voice that instant and said ' What that man asks is not to be refused ' and the petition was immediately granted."

Fosbrooke continues

" The ex-Emperor also liberated many others from time to time, at the request of Dr. Jenner, even whole families. Indeed he never refused any request made by Dr. Jenner who, of course, observed proper delicacy in not applying too often."

Wickham (John) is described in Foster's *Alumni Oxonienses* (Vol. IV) [9] as the son of John Wickham of Sherborne, Dorset, cler. who matriculated at Oriel College, Oxford, on November 3, 1791, aged 18, B.A. from New College 1798, M.A. 1798. B.Med. 1801, of Batcombe J.P. He had been elected a Radcliffe Travelling Fellow in 1801. Sir Farquhar Buzzard, Regius Professor of Medicine in Oxford writes privately.

" The fellowship in those days was tenable for 10 years and was worth £300 a year."

The author of *A Picture of Verdun* [14] relates that

" At the request of Jenner, Mr. Williams who has since published an account of his stay in France, was allowed to return from his captivity." (I have not seen this account. J. A. N.)

Baron relates that on several occasions Jenner was able to procure the release of gentlemen who were detained on the Continent. One was Sir George Sinclair, Bart., the son of the celebrated Sir John Sinclair, who had gone to prosecute his studies in Germany. He was at that time in Vienna and his friends were anxious that he should have a passport to return through France or Holland. This was obtained by a direct application to the Emperor of Austria which was transmitted through Baron Jacobi, the philosopher, who from 1807 to the time of his death was President of the Academy of Sciences in Munich.

The *Dictionary of National Biography* account of Sinclair says that he went to Göttingen and was arrested as a spy. He was brought before Napoleon who examined him and ordered his release. In 1826 Sinclair issued a privately printed *Narrative* [10] of the interview (Edinburgh, 1826, 8vo). This is the subject of a letter from his father to Sir William Knighton [11] dated from Edinburgh January 29, 1826.

" My eldest son had a most singular adventure with the Emperor Napoleon, immediately previous to the Battle of Jena ; and he has been induced to draw up a short narrative of that event (in 28 pages octavo) for the purpose of supplying ' *the Author of Waverly* ' with ' *new materials* ' for his intended history of that extraordinary character. Some copies of that Narrative have been printed for private circulation. I beg to know, whether I may take the liberty of sending a copy of it to you to be submitted to his Majesty's perusal. It throws some light not only on the character of Napoleon but on his mode of carrying on a war ' *on the principles of a game of chess* '."

Sir George Sinclair (1790–1868), M.P., was a Member of Parliament who supported the Emancipation of Slaves and the Reform Bill. He was a friend of Hume and Sir Frances Burdett. While M.P. he found time to attend the Edinburgh lectures of Dr. Hope on Chemistry, and Dr. Knox and Dr. Monro on Anatomy.

Jenner was also successful in a similar appeal to the King of Spain on behalf of the son of W. D. Powell, Chief Justice of His Majesty's Court of the King's Bench in Upper Canada. This young man who was nearly related to Mr. Murray, Secretary to the Royal Jennerian Society, was captured at sea by the Spanish. He was sentenced to ten years' confinement and hard labour in the Castle of Omoa, a seaport of Mexico. Dr. Jenner directly memorialized the King of Spain so that young Powell was released, and on February 19, 1808, gratefully acknowledged his obligation to Jenner.

Jenner's name carried a charm potent enough to disarm the hostility of belligerent States. English travellers left our shores not with a passport signed by a Minister of State but with a simple certificate bearing the name of Edward Jenner, testifying that the parties were known to him and were voyaging to distant lands, in pursuit of

health or science or other affairs totally apart from the concerns of war, and that in his opinion they were entitled to protection and freedom. Baron continues

" Probably there was not a civilized nation in the world that would not have paid respect to such a document."

He gives an example of such a certificate :—

" I hereby certify that Mr. A. the young gentleman who is the bearer of this, and who is about to sail from the port of Bristol on board the Adventure, Captain Vesey, for the island of Madeira, has no other object in view than the recovery of his health.

(Signed) Edward Jenner
Member of the N.I. of France etc. etc.

Berkeley, Gloucestershire, July 1, 1810."

On sending this certificate Jenner added

" I beg you to put this letter in your son's possession ; and should the ship in which he sails, through the chance of war be captured by a French commander, I trust he will, at my solicitation, show Mr. A. every indulgence in his power : and that if he will cause it to be made known to the French Government, it will obtain for him a speedy release. I feel the more confident of the Emperor's kindness in this case, as his Majesty has hitherto been pleased to lend a favourable ear to my petitions on behalf of British captives."

There is scarcely a parallel in history except perhaps the incident which Procopius [12] relates of Chosroes I nobly rewarding a Greek physician by the deliverance of three thousand prisoners.

It must be remembered that every sea-captain of every nation knew the debt that seamen and sea travellers owed to Jenner. We can scarcely realize the dreadful menace of smallpox introduced into a ship's company on one of its long sailing voyages round the Cape of Good Hope to the East Indies, or round the Horn to the Pacific Coast of America. From Dutch records [13] we learn that in 1804 vaccine had arrived in the Dutch East Indies by the good offices of General de Caen, Commander in chief of the French troops east of the Cape of Good Hope, Governor of the Isle de France and Réunion who had sent a Man-of-War Marengo, late in 1803, to Batavia with a supply of vaccine. Thus Jenner's beneficent gift to humanity was quickly spread across the artificial boundaries of nationalism.

There remain two other détenus who owed their freedom to Jenner's intercession with Napoleon. These were Mr. Gold and Mr. Garland. Jenner's later applications to the Emperor were transmitted through the hands of Corvisart who was in Baron's words

" exceedingly punctual in making all Jenner's requests known to His Majesty."

In a letter dated Paris, Dec. 5, 1809 [15], Corvisart reports that the Emperor has permitted him to reply

" that he has ordered the liberation of the two gentlemen (MM. Garland and Gold) in whom you are interested."

Corvisart then asked Jenner to do something for him in return on behalf of a French prisoner who had been sent back to France on parole from England. Baron adds

" His best efforts were, I believe, exerted for Corvisart's young friend, but unhappily, Jenner's influence with the British Government was not equal to that which he enjoyed with the Court of France."

This incident must be the subject of Baron's reference

" I remember finding him seriously distressed likewise by the fate of a young French officer, in whose welfare he took a deep interest. Captain Husson belonged to Dupont's army and was one of those who capitulated after the defeat of that General at Baylen. Jenner felt for young Husson as for a son ; and exerted himself with unremitting earnestness to procure his liberation.

"Unfortunately as I have already stated, his influence with the British Government was not so great as it was at one time with that of France. Either by direct appeals to the Emperor or through the medium of Corvisart and Husson he had succeeded in procuring the release of many persons. He observes in a letter to a friend that he feels the feebleness of his influence the more keenly from the following unfortunate occurrence. 'M. Husson one of the medical gentlemen above referred to, has a brother, Captain Husson, a prisoner of War in this country. I petitioned for his release. It was the first request of the kind I had made to the British Government; and it seemed to meet with a favourable reception. This joyful intelligence I communicated to Captain Husson: when most unexpectedly instead of acquiescence, a refusal arrived. This threw him into a state of desperation, and in the midst of it he broke his parole and is now in a state of misery and confinement on board a prison-ship at Chatham. This hurts me excessively: as I cannot but look on myself as in some measure the innocent cause. I shall again exert myself for Captain Husson, conceiving that my first application could not have been well understood'."

Baron goes on to say

"The second application I believe was successful. At least he concludes a letter to myself dated the 5th of April 1811 with these words, 'This day I received a letter from town informing me that my petition to the Prince on behalf of Captain Husson had been favourably received'."

Baron says that M. Husson (who wrote of Jenner and vaccination in the *Dictionnaire des Sciences Médicales* in the 1821 edition somewhat disparagingly)

"thought it not credible that they (the British Government) could refuse to the author of vaccination what the French Government had granted to him".

Mr. Garland is identified as Nathaniel Garland of Michaelstow Hall, by a reference to him as "a gentleman of considerable property in Essex" [17] and by his grandson, Dr. E. Blake Garland of Bristol, who has kindly placed at my disposal some notes made by his uncle the Rev. Nathaniel Arthur Garland, sometime Vicar of St. Matthew's, Tulse Hill, London. These notes were published anonymously (although the writer makes his identity clear) and "for private circulation only" (undated) under the title *Oddments from a Commonplace Life*. The booklet begins

"Returning through France from the 'Grand Tour' my father was made prisoner by Napoleon and was detained for the next eleven years, at Melun, Verdun, Valenciennes, etc. At one of these places he fell in with the Cope family, also 'detained', and in March 1814, was married to Ann their only daughter, at Orleans, by the Rev. Lancelot Lee, another 'détenu', afterwards Rector of Wootton, Oxfordshire. My father was then thirty-nine and my mother twenty-five."

Nathaniel Garland was born on 31st December, 1774, was sent to Eton and afterwards to Christchurch, Oxford, as a gentleman commoner matriculating on 15th November, 1793, at the age of eighteen. He did not wait long enough at Oxford to take his degree but started on the Grand Tour when he was about 20.

In *Oddments* the author, who was the second son of Nathaniel Garland, gives the following interesting account of an incident in his mother's life. When she was a girl of 14

"her father insisted on her presenting a petition to the Emperor Napoleon, asking that they might be transferred from Valenciennes (or Melun or Verdun) to Orleans. 'Every drop in me' she said long after to her youngest daughter, then a child, 'rebelled against such a proceeding'. So great was her aversion to Napoleon. But her father's will was law and it was arranged, with the consent of the Authorities, that the beautiful English girl . . . should be stationed at the corner of the street which the Emperor was to pass in State. Dressed in white, she stepped forward as the Imperial carriage appeared. Napoleon took the petition from her hand quite graciously, and the next day sent an aide-de-camp with a message of consent. He was always very appreciative of beauty."

No mention is made in *Oddments* of Mr. Garland's final release from internment. It is interesting to note that Mrs. Garland presented her petition to Napoleon in 1803 when she was 14 years old. She and her husband were still "détenus" eleven years

later when she was married in 1814. Yet Corvisart wrote to Jenner in December 1809 telling him that the Emperor had ordered the liberation of MM. Garland and Gold. Clearly the order referring to Garland was mislaid with that referring to Gold.

The prisoner who is of the greatest interest to this Section of the History of Medicine is Mr. Gold. Francis Gold was the son of a Bristol apothecary. He studied at the Bristol Infirmary and in London, becoming a member of the Corporation of Surgeons in 1801. In the same year he went with the Army to Egypt as a hospital-mate and was posted to the 61st Foot (now 2nd Bn. Gloucestershire Regiment) in General Baird's division.

At the Peace of Amiens in 1802 he resigned his commission and he describes how

" After the memorable expedition to Egypt under Sir R. Abercrombie to which I was attached, I obtained permission to return to England by way of the Continent. At the commencement of the present War I happened to be in France and was detained."

Actually he arrived in Paris on the evening before the decree was issued for detaining the English in that city. Gold was made a prisoner and was sent for a time to the fortress of Verdun. During the last two years of his nine or nearly ten years' detention he was appointed Surgeon to a depôt of Seamen (? captured British sailors) at Saar Louis [18]. Gold was singularly unfortunate in the length of his internment for in 1809, six years after his original detention, Corvisart wrote telling Jenner that Napoleon had ordered his release. Gold was not liberated, however, until 1812, when the order was found, after much inquiry, thrown aside in the office by the negligence of a subordinate Government official.

Soon after his return to Bristol Gold fitted up two rooms in the Cathedral Cloisters where he established a school of anatomy. It was in one of these rooms that some years previously the famous actress, Mrs. Robinson, was born, who afterwards captivated George the Fourth when she was playing the part of Perdita. The present Cathedral pulpit stands very nearly on the spot once occupied by the house.

During his captivity Gold translated one of the earliest and best books of mountaineering in the Pyrenees, Ramond's *Travel in the Pyrenees*. As a piece of translation this work of Gold's ranks high. He has kept close to the original, preserving admirably the lively and enthusiastic descriptions of Ramond whose French he has turned into smooth and unmistakable English. This book was published in 1813. He also translated Bichat's *Physiological Researches on Life and Death* in the following circumstances. Bichat had visited Great Britain and showed his experiments at the Medical Schools of London and Edinburgh. Dr. Kentish, Physician to St. Peter's Hospital in Bristol, was so much impressed by Bichat's work on life and death that he determined to publish it in an English translation and had begun the work.

" But at this period ", Kentish writes, " I became acquainted with Mr. Francis Gold, Surgeon, who had just returned (i.e. end of 1812) from a long confinement in France. I mentioned the circumstance to him, as it accorded with his views he undertook to translate the work which is now in the press."

Having twice applied unsuccessfully for the post of Surgeon to the Bristol Infirmary (in 1812 and 1816) in 1819 Gold relinquished his profession and went to London with the intention of turning painter.

However, by May 31, 1820, he had returned to Bristol and on that date he wrote to his friend Richard Smith—

"My dear Smith—

I have lately been making some stay in London with a view to reconnoitre the land of Art. I find that the land is a bad land and moreover that the grapes thereof are sour : on which twofold account I have resolved to retrace my steps thence as quickly as may be."

But he did not remain in Bristol, for in 1821 he was appointed an Assistant Surgeon by the Hon. East India Company on the Bengal establishment. In a report [18]

to the Honble. Court of Directors of the H.E.I.C. John Borthwick Gilchrist, who describes himself as Hindoostanee Professor in London and Director of the Oriental Institution under the patronage of the H.E.I.C., gives details of the progress of the students under his charge. In the list of medical students the rapid progress made by some of them is specially commented on ; that of

" Mr. Gold is very remarkable ; he not having yet attended above one month of the current course, when he has already reaped a stock of practical knowledge that very few pupils ever attain in double that time."

The India Office records [21] show that after his appointment in 1821 Francis Gold was stationed at Meerut in 1822. In 1825 he was appointed Assistant Surgeon, 31st Native Infantry and in 1826, Assistant Surgeon, 34th Native Infantry. He held this position until his death at Dougah in 1832.

REFERENCES

1 Baron, J., " Life of Jenner ", **1**, 602. London, 1838.
2 Duff-Cooper, A., " Talleyrand ", p. 153. London, 1935.
3 Doyle, J. W. E., " Official Baronage of England ", **2**, 186. London, 1886.
4 Mowat, R. B., " The Diplomacy of Napoleon ", 164. London, 1924.
5 Russell, Lord J., " Memorials and Correspondence of Charles James Fox ", **4**, 173. London, 1857.
6 Anon., " A Picture of Verdun or the English Detained in France. From the Portfolio of a Détenu ", **1**, 187. London, 1810.
7 Baron, J., *op. cit.*, **2**, 35.
8 Fosbrooke, T. D., " The Berkeley Manuscripts ". London, 1821.
9 Foster, J., " Alumni Oxonienses ", **4**. Oxford, 1888.
10 Sinclair, Sir G., " A Narrative ". Edinburgh, 1826.
11 Aspinall, A., " Letters of King George IV ", **3**, 138, No. 1226. London, 1938.
12 Gibbon, E., " Decline and Fall of the Roman Empire ", **7**, 127. (Bury's Edition.)
13 Schoute, D., " Occidental Therapeutics in the Netherlands East Indies during the Centuries of Netherlands Settlement (1600–1900) ", p. 94. Batavia, 1937.
14 Anon., " A Picture of Verdun ", *op. cit.*, **2**, 68.
15 Baron, J., *op. cit.*, **2**. 115.
16 Drewitt, F. D., " The Note-book of Edward Jenner ". London, 1931.
17 Anon., " A Picture of Verdun ", *op. cit.*, **1**, 187.
18 Richard Smith MSS. in Bristol Royal Infirmary.
19 Munro Smith, G., " History of the Bristol Royal Infirmary ", p. 375. Bristol, 1917.
20 Kentish, E., " An Account of Baths and a Madeira House at Bristol ". London, 1813.
21 Private Communication from Mr. Ottewill, Keeper of Records, India Office. (Jan. 13, 1939.)

Section of Surgery

President—C. H. S. Frankau, C.B.E., M.S.

[*January* 4, 1939]

Swallowed Foreign Bodies

By A. H. M. Siddons, F.R.C.S.

I shall only consider foreign bodies which have passed through the œsophagus, and indicate the likely fate of common objects which are swallowed in everyday life.

The questions which are always arising are: should I remove this foreign body? and how long is it safe to leave it without operating? It is these, which I will try to answer. I believe there is a considerable difference of opinion on these points.

Although a fairly large number of remarkable individual cases have been reported, I have found little published work, bearing directly on this aspect of the subject.

To form the basis for this paper, I have consulted the records of three London hospitals, and collected all the cases, of which they have complete records. These hospitals are St. George's, the Royal Waterloo, and the Belgrave. A large number of my cases are children. These hospitals have a high proportion of children's beds, and it is children and lunatics who most frequently swallow foreign bodies.

My total of 126 cases only include admissions to hospitals—cases selected by surgeons as sufficiently dangerous to require treatment as in-patients. I emphasize this point, because it is not possible to draw accurate conclusions from these figures as to what percentage of *all* swallowed foreign bodies require operative removal. It would indeed, be quite impossible to obtain such statistics, as so many cases do not reach the hands of a doctor at all. As only the apparently dangerous cases are admitted to hospital, any figures such as mine must exaggerate the risks.

Of my 126 cases, in 107 or 85%, the foreign bodies were passed naturally. In only four did perforation or obstruction occur. The remaining thirteen foreign bodies were removed as the surgeon considered it dangerous to leave them, or because it did not appear to him that they would be passed naturally.

Table I.—Swallowed Foreign Bodies.

Passed *per vias naturalis*	107	
Perforations	3	
Obstructions	1	died
Removed as considered dangerous to leave	15	1 died
Total number of cases	126	2 deaths

Henderson and Gaston [3] have reviewed such cases attending a hospital in Boston. They found nine cases of perforation out of about 800 cases most of which were not admitted to the hospital; that is about 1% perforated. They also emphasize the fact that many people who swallow foreign bodies never seek medical advice, and that the figure of 1% for perforations is really unduly high.

I have divided my cases into three groups: first, blunt objects; secondly, long objects; and thirdly, sharp objects. Each group requires separate consideration, as it may give rise to different complications.

(1) *Blunt objects.*—It is interesting to notice how long these stop in one place in the alimentary canal, only to progress again for no apparent reason. One would surely expect a foreign body which had failed to get through the pylorus for a whole day, never to do so; but this is not the case. In some of these cases, the foreign bodies were watched in the stomach for several weeks, and then without warning went on their way. The average length of time for the foreign body to pass naturally in this entire series was six days. In each group, the figure was about the same.

What is much more important is, while they are stationary they do not seem to do any harm. There are many records of lunatics, and professional swallowers who have retained foreign bodies in their stomachs for very long periods, and have suffered no ill-effects. In none of my cases was there any record of any signs or symptoms of damage except in one where a foreign body arrested in the ileocæcal region caused intestinal obstruction.

TABLE II.—BLUNT FOREIGN BODIES.

	Total	Passed	Operations
Shillings	2	2	
Halfpennies	13	12	One removed from stomach 12th day.
New 3d. bit	1	—	Removed from stomach 13th day.
Farthings	9	7	Removed from ileocæcal region 11th day. Two removed from stomach 1st day.
Dentures	6	4	Removed from stomach 7th day. Removed from stomach 14th day.
Miscellaneous: closed safety-pins whistles, rings, &c.	29	27	Wrist watch removed from stomach 2nd day. Rubber teat removed from ileum 9th day.*
	60	52	Eight operations. One death.

* Caused intestinal obstruction. Died day after operation.

Of the 60 cases of blunt foreign bodies in my series, eight were operated on, and the object removed. With the exception of the one case I have just mentioned, there were no signs or symptoms suggesting that they were doing any harm. These operations were undertaken as the surgeons were of the opinion that the foreign body would not pass naturally, and were all performed within fifteen days of the object being swallowed. Had they been left a few weeks longer probably no harm would have come, and most of them would have been passed naturally. I think that there are very few foreign bodies, able to pass down the oesophagus, that will not pass through the entire alimentary tract, providing they are not sharp or unduly long.

Given plenty of time, only a very few will stick, and most stop at the pylorus. If they pass the pylorus, the ileocæcal region seems to be the only other likely site of arrest.

There are no hard and fast rules as to what sized foreign bodies will pass. It is interesting that a halfpenny which is 1 in. in diameter, seems to pass easily in a child

aged three. There were four children aged 3 in my series who swallowed halfpennies, and they all passed them. There were two aged 2 who swallowed halfpennies. One of these passed naturally, but the halfpenny was removed from the stomach of the other one after thirteen days. Other authorities seem to agree that this seems to be about the crucial age for halfpennies.

To most surgeons the removal of a foreign body from the stomach means gastrotomy, but Chevalier Jackson [4] has stated that any foreign body small enough to pass down the oesophagus can be brought back from the stomach by means of a gastroscope. He admits that this may be a difficult proceeding. The use of the rigid gastroscope which he uses is not so safe as the use of a flexible diagnostic gastroscope. Tucker [6] has invented an ingenious flexible gastroscopic forceps. with which he fishes for foreign bodies under the X-ray screen. Now that the use of the flexible gastroscope is becoming so widespread it is possible that a practical and easy technique will soon be worked out.

At present, however, most surgeons remove them by abdominal operation. This may be very difficult, especially in young children, and it must carry a small but definite mortality. Jackson [4] estimates it at 5%. There were twelve gastrotomies in my series, with one death.

The value of knowing the exact site of the foreign body before operation is enormous. If possible it should be localized by the patient swallowing sufficient opaque fluid to outline the stomach. If more than a few minutes are allowed to elapse between the X-ray and the operation, it is only too common to find that the object has moved.

Occasionally one has to operate on a foreign body which is in the second, or third part of the duodenum. This will be even more difficult than a gastrotomy. If possible it should be milked back into the stomach, or first part of the duodenum, from which site it can be more safely removed.

A case in which the foreign body caused obstruction has been mentioned. This is a very rare complication, but the only one which is likely to occur from the blunt type. In most of the published cases of obstruction there has been more than one foreign body, or it has been due to a hair ball.

The patient was a child, aged 1 year, who had swallowed the rubber valve from her feeding bottle. The mother was not certain of this fact, and did not mention it until six days later when the child was taken to hospital with vomiting and constipation. No foreign body was seen on X-ray examination as it was not opaque. The obstruction was temporarily overcome with enemata; but three days later recurred and enemata failed to relieve the condition. A laparotomy was performed, and the foreign body removed from the terminal ileum, but the child died fifteen hours after operation. The rubber valve had apparently been acting as a ball valve, as gall-stones may in adults [7].

This raises the question as to what diet should be given to patients who have swallowed foreign bodies. It seems to be usual to give them large quantities of bulky foods. In a case such as the one just described, this is definitely dangerous, and may hasten the obstruction. Even in the case of sharp foreign bodies, I do not believe such a diet serves any useful purpose, and I advise these patients to have an ordinary diet and to take no purgatives.

This case is also interesting as it is an example of a foreign body which was not opaque to X-rays. These are not very common, though it is unusual to be able to see a fishbone on an X-ray examination.

(2) *Long blunt objects.*—These include screws, nails, and Kirby grips, &c.: I am under the impression that the commonest of these is the Kirby grip or hair-clip which is used to-day. There are, however, only three of these in my series. I think they must be swallowed more frequently by private than by hospital patients.

These long foreign bodies usually pass the pylorus but they find the fixed curves of the duodenum a difficult hazard. X-rays show them lying transversely across the vertebral column at the level of the duodenum, or perhaps vertically just to the right of the vertebral column when they are in the first and second part of the duodenum. If they get past the fixed duodenal curves, they usually find no other obstruction.

Unfortunately the length of the foreign bodies in my series has not always been recorded, but it is interesting to know that there was a bodkin 3½ in. long which was passed by a child, aged 6, in eleven days. There was also a Kirby grip 2½ in. long which was passed by a child, aged 2, in eight days. These seemed to be about the limits of length of foreign bodies which were passed at these ages, and again they are in agreement with other authors [5].

TABLE III.—LONG FOREIGN BODIES.

	Total	Passed	Operation
Kirby grips	3	3	
Screws	7	7	
Nails	7	6	One removed from cæcum 2nd day.
Bodkin 3½ in. long	1	1	
	18	17	One operation.

In my series there were only 18 foreign bodies which I have classed as long, and the only one of these that was operated on was removed from the cæcum on the second day, and I believe would have been passed naturally had it been left. My general impression is that these long foreign bodies become arrested at the duodenum more often than my figures suggest. Apart from this collection of cases, I have come across a good many cases where Kirby grips remained in the duodenum for several weeks, and here they may sometimes perforate.

More or less blunt objects of this type perforate by ulcerating slowly through the gut wall. This usually gives rise to a localized peritonitis, for the slow ulcerating process is accompanied by an inflammatory reaction in the overlying peritoneum, which keeps the infection localized. Occasionally, however, there is a general peritonitis [4].

Ginzberg and Beller [2] have collected a series of 13 cases of perforations by fish-bones, and similar non-metallic foreign bodies. They found that these objects perforated by the same slow ulcerative process, and as a result, they gave rise to a localized abscess in most cases. In only two of their 13 cases was there generalized peritonitis.

As the process of perforation is a slow one with this type of foreign body, one can afford to wait at least a week or ten days, while the body is impacted in the duodenum. The danger of perforation in this time is extremely small. If they remain stationary for more than ten days, they should be removed.

(3) *Sharp foreign bodies.*—These include needles, ordinary pins, and open safety-pins, the last present a special problem.

There were 40 patients who were admitted to hospital having swallowed sharp foreign bodies other than open safety-pins. 35 of these were needles, or pins. Not a single one perforated. Three of these patients were operated on, and the foreign body removed, as the surgeon did not consider it safe to leave it, though there were no signs or symptoms of perforation. The remaining 37 patients passed them naturally.

Surely these figures show that sharp, like blunt, foreign bodies should be given a chance to pass before resorting to operation.

TABLE IV.—SHARP FOREIGN BODIES. (*Excluding Open Safety-pins*)

	Total	Passed	Operation
Pins	31	28	Three removed from stomach by early operation.
Needles	4	4	
Miscellaneous: gramophone needles, tin-tacks, &c.	5	5	
	40	37	Three operations

Also two patients in whom sharp foreign bodies were found by X-ray in the tissues of the abdomen, presumably swallowed.

In two patients in this series sharp foreign bodies were found more or less accidentally in the abdominal tissues. Presumably these must have been swallowed, though the patients were not aware of the fact.

Case 1.—A patient, aged 18, came to hospital complaining of abdominal pain shooting from the epigastric region to the right side. She had had attacks of this pain for fourteen years, the attacks lasted about ten minutes each time. She had had eight or ten attacks a year. An X-ray revealed a wire 1½ in. long, lying beside the 3rd lumbar vertebra. She was operated on, and the wire removed from the retroperitoneal tissues beside the aorta. There was a small area of staining on the posterior wall of the stomach, and it was thought that this was due to rust, and marked the probable site of perforation.

Case 2.—A man, aged 41, was being treated in hospital for ulceration and œdema of the legs. An X-ray was taken of his abdomen, and two needles were seen. As far as could be told, he had had no symptoms from these at all, and he did not remember having swallowed them. He has been in good health for eleven years since that time, and still has no symptoms.

TABLE V.—OPEN SAFETY-PINS. (8 cases.)

Passed	3		
Perforated	1	Perforated stomach.	Removed successfully.
Removed by early operation ..	4	Two from stomach.	One died.
		One from duodenum.	
		One from jejunum.	

The problem of the open safety-pin.—My series only included eight swallowed open safety-pins. Four of these were removed by early operation, with one death. Of the other four, one perforated the stomach wall, and was removed safely. And the other three were passed naturally. Eight cases are not sufficient from which to evaluate the risks, but there is no doubt that they are greater with open safety-pins than with any other sharp foreign body I have come across.

If the open safety-pin starts off through the pylorus, the blunt end leading, trailing its point and keeper, it will probably pass. If it starts the other way round, it will clearly catch, and may perforate. Jackson [4] describes one case in which he saw through the gastroscope the keeper of a safety-pin stuck through the pylorus' while the point pierced the stomach wall. Each peristaltic wave seemed to drive the point further in. I think this picture explains to us very clearly why an open safety-pin is so much more dangerous than the simple pin or needle. The bowel has no blunt end on which to work in the case of a simple pin or needle; whereas when the point of a safety-pin has caught on a fold of mucous membrane, the contractions of the bowel working on the blunt end will drive the sharp end in deeper and deeper.

In order to decide on the best line of treatment, one must try to weigh the dangers of leaving the pin to pass, with those of removing it. Jackson's estimate that the mortality of gastrotomy is 5% has already been quoted. He also states that 95% of open safety-pins if left, will pass safely. If we accept these figures, there can be

no doubt that we should give them a chance to pass, rather than remove them, because we shall be able to save many of the 5% which do not pass naturally.

Jackson avoids taking either of these two courses by removing the pin with the gastroscope. In his hands this carries no mortality. It seems clear to me that if any foreign body is to be removed by gastroscopy, it is the open safety-pin, but in the absence of a surgeon experienced with the rigid gastroscope, it should be left, and its course followed with X-rays taken daily, which will show if the pin is stationary, by its relation to the bony points. A very careful watch should be kept for abdominal pain and localized tenderness. These indicate perforation; in which case early operation is essential, and I do not see why the results should not be as happy as they were in the one case that I came across.

This was a boy aged 6. He had no symptoms until the fourth day, when he suddenly complained of upper abdominal pain. There was no real rigidity, but vague tenderness in the upper abdomen. An X-ray with barium meal showed the point of the safety-pin perforating the stomach wall. The boy was operated on at once, and the pin removed without difficulty. It was found with its point sticking through the lesser curvature into the liver. There were no signs of peritonitis. The patient recovered without any post-operative complications.

I do not think that either the appendix or Meckel's diverticulum are common sites for the arrest of foreign bodies. These are occasionally found in the appendix at operation, but they do not play an important rôle in the ætiology of appendicitis.

There are reports in the literature of seven cases in which a foreign body was found in Meckel's diverticulum [1].

The rectum is not an uncommon site for arrest of foreign bodies, especially of the sharp variety. They can be felt with the finger, and can be removed with the proctoscope. Occasionally they perforate the rectal wall, for a fishbone or other foreign body is sometimes found in an ischiorectal abscess or fistula.

Summary and Conclusions.

Out of 126 cases there were only three perforations, and two of these passed unnoticed by the patient. There was one case of obstruction which died. The only other death was after removing an open safety-pin.

Nearly all blunt objects pass naturally, and should be given at least four to six weeks to do so. Very rarely they may cause intestinal obstruction.

Long blunt objects may become arrested at the duodenum where they may ulcerate through its wall. It is safe to leave them a week or so, but a watch must be kept for signs or symptoms of perforation.

Sharp objects usually pass naturally without complications. They should be left and watched carefully with X-rays. Pain or localized tenderness is an indication for immediate operation. If they do perforate, they do not give rise to severe peritonitis.

Open safety-pins are probably more likely to perforate than any other object which is commonly swallowed, but the dangers in this event do not justify immediate operation. They, like other sharp foreign bodies, should be given a chance to pass naturally.

REFERENCES

1 Eitel, G. D., *Minnesota Med.*, 1935, **18**, 52.
2 Ginzberg, L., and Beller, A. J., *Ann. Surg.*, 1927, **86**, 928.
3 Henderson, F. F., and Gaston, E. A., *Arch. Surg.*, 1938, **36**, 66.
4 Jackson, Chevalier, and Jackson, Chevalier L., "Diseases of Air and Food Passages of Foreign-Body Origin." Philadelphia, 1936.
5 Phelpps, *Minnesota Med.*, 1935, **18**, 52.
6 Tucker, Gabriel, *J.A.M.A.*, 1933, **105**, 1956.
7 Wilson, J. R., Unusual Case of Intestinal Obstruction, *Lancet* (ii), 1937, 1073.

Swallowed Foreign Bodies in Relation to Mental Hospital Practice

By T. D. Power, M.D.

I have lived in a public mental hospital for the past seventeen years. We have a permanent population of 2,000 patients and an admission rate of about 400 a year. In actual fact insane people do not swallow foreign bodies more often than their saner brethren, but this is because they are so carefully watched.

Broadly speaking there are five reasons why people swallow foreign bodies: (1) Entertainment; (2) Accident; (3) Ignorance; (4) Mischief; and (5) Suicide.

The *entertainers* are too well known to need comment. Many of them are illusionists, but doubtless a few do actually swallow the objects placed in the mouth.

Foreign bodies swallowed by *accident* probably form the bulk of the cases in surgical practice.

Case 1 was a simple-minded girl who swallowed a necklace in this way She put it into her mouth absentmindedly, as she herself stated, "It slipped down ever so easily." She passed it *per rectum* three days later.

Under the heading of *ignorance* are those cases which occur among infants. In mental hospitals those who have been insane for years return to the level of infancy, and such demented people will eat all sorts of rubbish, pieces of clothing and wood, stones and leaves. For this reason yew and laburnum trees are not grown in mental hospital grounds, for the leaves of both are poisonous. Among this group of "swallowers" is a man who for years has eaten newspapers. They have never done him any harm; indeed, in my opinion, far less harm than if he had read them.

We now come to the fourth category. Among the insane *mischief* is by far the most frequent motive for swallowing foreign bodies. These "swallowers" are remarkably sensible in conversation, but possess no powers of self-control. They are vindictive to a degree and they swallow foreign bodies with the object of giving as much trouble as possible to those who look after them and whom they are well aware are responsible for their welfare. Here are one or two illustrations:—

Case 2, a woman. During the last seventeen years she has swallowed a metal handle off a jug, numerous paper clips, a needle, two needles threaded on a piece of cotton, two pins, a piece of wire, a tin-tack, and a handle off a china cup. All these objects have been passed *per rectum* and in no instance did she need an operation. It is interesting to note that the two needles threaded took nine days to pass through the bowel.

Case 3, a woman aged 30. On August 14, 1930, she stated she had swallowed a needle and on August 17 an X-ray photograph showed a needle lying at the level of the 1st lumbar vertebra. On August 18 the needle was removed from the general peritoneal cavity. A small hole in the stomach was stitched up and a tube inserted. Patient made an uninterrupted recovery and was up and about on September 8. On December 27 of the same year she stated that she had swallowed another needle, and on January 1, 1931, a second laparotomy was performed by Mr. Handfield-Jones. This time two needles knotted together were removed from the stomach, the point of one having perforated the viscus. It was later discovered that the needles had been swallowed on different dates, so that the process of entanglement had taken place within the stomach. Again the patient made a rapid recovery and was up and about in a month's time. On April 9, 1931.

she again swallowed a needle, and seven days later a third laparotomy was performed. This time the needle was removed from the duodenum. Again convalescence was uneventful. Three years later the patient died of bronchopneumonia.

Patients of this sort swallow foreign bodies in order to make themselves a nuisance. It would seem, therefore, the wiser course to ignore such incidents if only one was certain that perforation would not occur. But how can one know? Case 2 passed needles through the bowels with ease, while Case 3 was apparently unable to do so. Another patient was completely cured of a similar habit by simply ignoring it.

Case 4.—This man did not swallow needles, but pushed them deeply into the muscles of his arms whenever he was angry or desired to give trouble. When he first came under my care in 1930 he had had needles removed from his arms on 14 occasions, but the operations had not kept pace with his fits of temper, with the result that there remained deeply embedded in the tissues of each limb about 18 needles. Now, I had decided during the war on an occasion when I had opened an aneurysm in mistake for an abscess, that I had no flair for surgery, and I had also recollections of hours spent in the operating theatre in the fruitless search for pieces of shrapnel. Consequently, I was determined that nothing would induce me to hunt for this man's needles. I told him that they would do him no harm and that I was not going to worry about them. That was eight years ago, and he has not pushed any more needles into himself since.

We now come to the last group of cases, viz.: those whose "swallowing" is motivated by the idea of suicide. Fortunately, few people attempt suicide in this way, hanging being the method most commonly adopted in a mental hospital. Occasionally, however, a patient will try and commit suicide by swallowing a foreign body. Here are some instances:—

Case 5, a woman aged 59. On September 1, 1927, I made the following note on her case sheet: "To-day, during the dinner hour, patient was seen to put a spoon well down into her pharynx. A nurse removed this with some difficulty, whereupon the patient stated that she had already swallowed a fork. The evidence seems conclusive that this statement is correct. She was definitely given a fork, and now no fork can be discovered. Morover, the number of forks in the ward is 51, whereas it ought to be 52." Next day an X-ray examination showed a fork in the stomach, prongs uppermost, and four days later the fork was removed by laparotomy. Six months later the patient again swallowed a fork and an X-ray examination showed it to be lying prongs uppermost in the middle third of the œsophagus. A further examination four days later revealed that the fork had moved to the lower end of the œsophagus and next day Mr. Handfield-Jones opened the abdomen and removed the fork by pulling it through the cardiac orifice of the stomach. The patient died ten days afterwards from abscess of the lung. Food had undoubtedly found its way into the trachea. The patient from first to last wanted to kill herself.

Case 6 was another suicidal case. She was a woman aged 29. On January 24, 1932, during dinner, she seized a spoon, broke it between the bowl and shaft, and thrust the handle down her throat. Six days later an X-ray examination revealed the spoon lying somewhere in the pelvis and next day she passed it *per rectum*. The handle was 4 in. long but, beyond running a slight temperature for a couple of days, the patient suffered no ill-effects. However, eight months later she deliberately choked herself by stuffing a quantity of food down her throat. Immediate tracheotomy failed to save her life.

Case 7, another woman, also swallowed the handle of a spoon, but she swallowed with it two pieces of wire which she had broken off from the springs of her bedstead. In due course all the foreign bodies were passed *per rectum*. After making further suicidal attempts she eventually recovered her sanity. The fact that many such insane people do recover is some compensation to the surgeons who from time to time are called upon—often at great inconvenience—to operate on them.

The Injection Treatment of Hernia

By A. E. Porritt, M.Ch.

One hundred years ago Heaton of Illinois worked out, practised, and wrote a treatise upon a logical scientific treatment by injection—a method which later achieved considerable popularity in America and on the Continent. Towards the end of last century advances in anæsthesia and antisepsis made operative treatment so much safer that surgery has until recent years held unquestioned sway. For the last seven or eight years, however, interest has reawakened in injection methods considerable research has been undertaken, a mass of literature has appeared and the technique is widely practised and accepted, having produced a striking number of satisfactory results. And all this in countries other than our own.

It was these facts which first prompted me, admittedly then a sceptic, to try out the method some four and a half years ago. The rationale is simplicity itself—to fill up the inguinal canal with fibrous tissue, which is formed as the result of injections of a chemical irritant and which either prevents the descent of a sac into the canal or of contents into a pre-existing congenital sac.

Here is a method which, *in selected cases*, achieves results certainly as good and probably better than operation without nearly as many risks. The patient, if given the option, sees the obvious advantage of a method which is ambulant, avoids loss of work, and involves minimal expenditure of time and money, rids him of the bogies of an anæsthetic and an operation, and at the same time is efficacious, free from any major risk, and relatively painless.

Choice of case.—The hernia *must be completely reducible*. I personally have dealt chiefly with inguinal herniæ—indirect, direct, and recurrent—but have more recently had equally good results with femoral herniæ. Elsewhere, umbilical and ventral herniæ are also treated as a matter of course by injection. Sex, apart from certain anatomical variations, matters not at all. The two outstanding requirements, apart from reducibility, are an external ring of reasonable size (that will not take two fingers) and an absence of excessive subcutaneous fat. The size of the hernia *per se* is of small importance. A very large ring makes truss control of the hernia difficult; excess fat increases technical difficulties and as there is usually excess extraperitoneal fat more necrosis than fibrosis is produced at the site of injection.

The patient must also be sufficiently intelligent to co-operate as he must not remove the truss during treatment. Hence children are not, generally speaking, suitable.

Patients with ascites, pregnancy, active venereal disease, hæmophilia, and infective skin conditions of the groin, are obviously unsuitable; and in those with undescended testis or a sliding hernia, injection is unwise.

I feel that cases of diabetes, chronic renal, hepatic, and pulmonary diseases, are especially suitable for treatment by this method.

The truss.—A truss must be worn for twenty-four hours a day during treatment, i.e. the hernia must be kept completely controlled. It should also be worn to a decreasing degree after treatment is finished to allow consolidation of the new and relatively soft fibrous tissue. Many types of truss have been recommended. From the mechanical and hygienic points of view I have yet to find a better than a vulcanized hard rubber pad attached to a steel spring similarly coated. This is clean, immersible

in water, gives a firm pressure and, if heated, is sufficiently malleable to be accurately fitted to the individual patient. I always insist on a preliminary period of wear both by day and at night, so that the patient may be thoroughly used to the feel of his truss before actual injections begin. Once treatment has started the truss is only removed by the surgeon at the time of injection.

Technique.—The injections are given with the patient lying on his back and relaxed. Pubic hair should, if necessary, be cut with scissors and not shaved, as the latter frequently leads to dermatitis under the pad of the truss. The needles used are 22 or 23 gauge with a medium bevel. The needle is inserted vertically to the skin at the site chosen. This is determined at first by invaginating the scrotal skin in the male and identifying the external ring with the tip of the finger. Later, surface landmarks or the palpable granulation tissue of previous injections will be the guides, and in the final stages a slight cough will serve to demonstrate residual weak areas. The needle on being inserted meets two resistances, the skin and the aponeurosis of the external oblique. It is immediately deep to this latter layer that the solution should be injected, after preliminary aspiration, to exclude the possibility of the needle point being in a vessel. Injections may begin at either the external or internal rings. I favour the former as localization at that point is so exact.

In direct and recurrent inguinal herniæ in the male and in indirect in the female the sites of injection are determined by anatomical landmarks and by gentle coughing to demonstrate obvious weak places. In femoral herniæ injections are made along a line marked out on the skin from the upper part of the middle of the femoral ring to the lowermost part of the bulge made by the unreduced sac when standing, the needle being directed inwards towards the middle line and the femoral vessels held out of the way by a protecting finger.

The frequency of injections will vary with the individual's reactions, but usually at least two per week can safely be given. The number of injections necessary averages 10 to 12, the maximum I have given being 34, and the minimum 3, to effect a cure.

When after several injections a cough produces no bulge when lying down, the patient is similarly tested when standing up. If all is well, he wears his truss night and day for a further fortnight ; it is then discarded at night only for a fortnight, then worn for another two weeks at work only, and finally completely discarded. The total period during which injections are given is as a rule five to six weeks, but the truss will be worn to some extent over a period of about three months.

Long lists of complications have been compiled, but personally I have seen few. Local pain, momentarily at the time of injection and a few hours later of varying intensity and duration, occurs in about half the patients. This is seldom sufficient to interrupt normal activities. Local inguinal swelling—probably a chemical lymphangitis—may occur, particularly after the first few injections. It subsides rapidly. Pain in the testicle during injection means the needle is probably in contact with the cord and it should be moved away. Pain in the abdomen means an intraperitoneal injection. In this case the injection should be stopped immediately.

The immediate results of intraperitoneal injection may be alarming. The patient shows all the signs of severe shock coming on in a few moments, but the recovery is equally rapid. Of the half-dozen I have perpetrated, only one has not cleared up spontaneously within an hour without any late bad effects, and that one, poor fellow, got into other hands and was operated upon for acute appendicitis !

Transient hydrocele of the cord may occur, especially if injections are begun at the internal ring. Atrophy of the testis I have yet to see and impotence and sterility yet to hear of.

Solutions.—In my first series I used a modification of Mayer's solution, the basis being carbolic acid and zinc chloride. The dose is 0·5 to 1 c.c. This solution is efficient, but I think too caustic. Since, I have used a number of solutions. The American solutions—sylnasol, proliferol, &c.—are excellent from the point of view of their painlessness, but I think inferior in their effect. I tried the addition of novocain to Mayer's solution, but this was a failure, either the heating of the solution or the chemical interaction of the constituents producing some very potent breakdown product which led to marked reactions, though incidentally excellent results. I am now using, and am very satisfied with, the solution recommended by Watson consisting of butyn and urea hydrochloride. This is given in 1–2 c.c. doses, is practically painless, gives no general systemic reactions, is stated to be non-toxic if injected intravenously or intraperitoneally, and gives a maximum fibroblastic reaction without excessive exudation.

Results.—My first published series of 100 cases (*Lancet*, 1937 (ii), 835) contained two failures and five so-called recurrences, which I ascribed either to bad selection or inadequate treatment. These five responded well to further injections and have remained satisfactory. In the original 100 there have been ten further "recurrences", all but two of which have been easily put right by further injections. The two have been operated on and in this connexion I should like to say that I found remarkably little difficulty in dealing with them. The fibrous tissue beneath the external oblique was well organized and relatively easily dissected from the cord and sac.

This hospital series has now increased to 246 (266 herniæ), the number of injections being 2,115. This means an average of eight injections per patient, but some of these are as yet unfinished. Amongst the subsequent 150 I have had again two definite failures, and seven have required further injections after having reached the stage of totally discarding the truss for varying periods. With more cautious selection and added experience in technique, I feel it safe to say that at least 95% of the patients injected are being cured. As far as possible, cases are being followed up for three years and the late results seem eminently satisfactory. In the majority of the recurrences, a few more injections have rapidly dealt with the condition—a point vastly appreciated by the patient.

In conclusion I should like just to mention the economic aspect. In my previous communication, *vide supra*, I showed by very rough calculations how this treatment, if generally adopted, might effect a saving of a minimum of half a million pounds annually to hospitals, patients, public health bodies, and medical aid societies. I have been advised since that this was a very moderate estimate, but even these minimum figures are weighty enough. The economic aspect becomes even more important when one considers that the class chiefly concerned contains young to middle-aged able-bodied men—the productive workers of the country. So much so is this recognized now in America that large industrial concerns and insurance companies, when dealing with claims for "rupture", are more and more tending to advise injection treatment where possible. The saving to the individual and the freeing of hospital facilities in favour of more serious conditions are obvious, and one imagines that more general use of the method might solve a very definite problem in the Services.

Finally, may I say that here is an alternative to operation in certain cases, an alternative that gives good results with minimal risks. I would suggest that we in this country have already lagged far behind in exploiting its possibilities, and that it merits a more general and extensive trial than it has yet received.

Section of Surgery

SUB-SECTION OF PROCTOLOGY

President—J. P. LOCKHART-MUMMERY, F.R.C.S.

[*November* 9, 1938]

Prolapse of the Blind End of a Colostomy through the Perineum Five and a Half years after Perineal Excision.—Sir CHARLES GORDON-WATSON, K.B.E., F.R.C.S.

The patient was a male aged 70. The rectum was excised in June 1933.

Pathological report.—The specimen measured 9 in. in length. A flat, semi-ulcerated growth, 1½ in. in diameter, extended half-way round the rectum, being situated on the posterior, right lateral and anterior quadrants. Its lower edge was 1½ in. above the ano-rectal line and there was 3 in. free margin above. No papillomata were present. There was no gross evidence of extrarectal spread.

Microscopic structure.—The tumour is an adenocarcinoma which has spread by direct continuity into the extrarectal tissues. Histological Malignancy Grade No. 3. No metastases were found in the regional lymph nodes but secondary carcinomatous deposits were found in an enlarged gland situated 2 in. above the upper edge of the growth.

After-history.—The perineal sinus did not close and a year later mucosa was visble at the perineal margin. A portion of this was then excised.

Further prolapse occurred, but did not cause much inconvenience and was kept up by a pad.

Recently there was a sudden increase of the prolapse which could not be reduced.

As the patient was in constant pain I decided to remove the prolapsed portion.

This was done on October 28 and the stump re-closed.

Solitary Diverticulum of the Cæcum.—G. GORDON-TAYLOR, O.B.E., M.S.

A specimen was shown from a male patient, aged 69, who was operated upon for a subacute abdominal condition in the right iliac fossa.

At the operation a definite lump was to be felt in connexion with the cæcum, and it was difficult at the time to decide its nature.

A right-sided resection of the colon was performed.

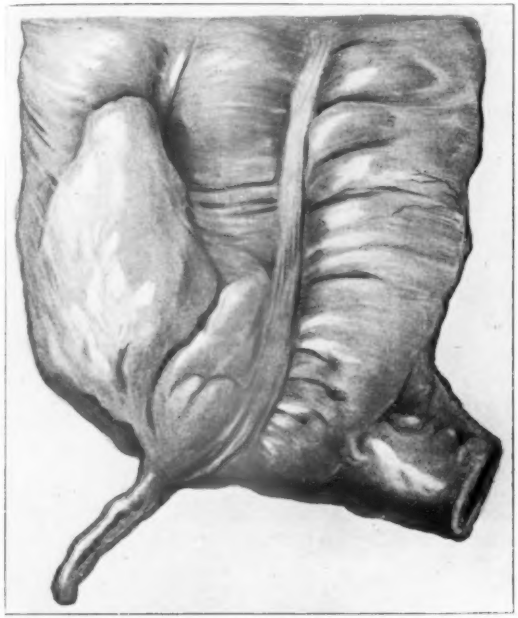


FIG. 1.—Cæcum from behind showing diverticulum on posterior wall.

FIG. 2.—Orifice of diverticulum viewed from mucous surface of cæcum.

The illustrations show a solitary diverticulum of the cæcum, of considerable size. No other diverticulum was noted in any other part of the colon.

Microscopic examination showed only intestinal epithelium, and no evidence of gastric mucosa.

Lipoma of the Colon.—P. LOCKHART-MUMMERY, F.R.C.S.

R. G., a man aged 42. Complained he had not had a normal stool for four months. He got painful peristaltic pains in the abdomen with desire to go to stool coming on frequently; stools, often three to four times a day, but unsatisfactory and accompanied sometimes by a little blood.

Symptoms all pointed to a growth, or obstruction of some kind, in the pelvic colon. Both a barium meal and enema X-ray showed a definite filling defect in the upper part of the pelvic colon; the sigmoidoscope passed the full length and showed no abnormality.

Operation (May 1932).—Abdomen opened by left lateral oblique incision. A largish tumour was found in the pelvic colon causing very considerable obstruction, the bowel above was dilated. Four inches of the colon were resected and end-to-end anastomosis performed with plain stitching.

The patient made an uninterrupted recovery.

The tumour was a lipoma growing from the submucous tissue of the pelvic colon and almost completely filling the lumen.

Extensive Ano-Rectal and Urethral Fistulæ with Plastic Repair.

By E. T. C. MILLIGAN, F.R.C.S. and A. H. MCINDOE, M.S.

Mr. E. T. C. Milligan.—The outstanding features of the case are :—

(1) The extensive damage done by prostatitis and urethritis through its spread into the ischiorectal fossa and perineal tissues.

(2) The futility of anything but drastic surgery when the disease is so widespread and moreover the extensive mutilation of such surgery.

(3) The confidence for the future treatment of difficult cases in the knowledge that plastic surgery can restore such damage in this region, once infection is removed.

M. M. Occupation : Seaman.

March 1932 : He was seen with multiple urinary sinuses in the perineum, extending from sacrum to scrotum. There was stricture of the urethra and frequency and pain on micturition due to cystitis.

Numerous operations for the cure of fistulæ, perineal abscesses and stricture had been performed in Belgium and America in the years 1912, 1913, 1914, 1917, and 1930. These had left the skin and tissue of the scrotum and perineum distorted, thickened and scarred. His troubles had resulted from gonorrhœal urethritis and prostatitis. The perineal fistulæ were found to communicate with the prostatic and bulbous urethra and to surround the anus completely, traversing both ischiorectal fossæ. The external openings were as far back as the sacrum, part of which had subsequently to be removed.

March 1932 : Before the difficult task of cure was entered upon, suprapubic bladder drainage was established.

April 1932 : The urethral stricture with urethral fistulæ and accompanying scar tissue was excised by the Hamilton Russell technique.

This resulted in a cure of the stricture but the floor of the urethra failed to heal from lack of tissue. The healed roof of the urethra was exposed from the apex of the prostate where the urethra had been rejoined for about $1\frac{1}{2}$ in. of the anterior urethra.

May 1932 : Acute pyelonephritis developed in the left kidney.

May 1932 : fistulæ in the ischiorectal fossæ were now opened up and found to lead to the prostate. The tracks, completely encircling the anus and the anterior wall of the rectum were exposed. No tissue remained between urethra and rectum.

June 1932 : More sinuses were found and opened up.

August 1932 : Tracks of fistulæ to prostate were dissected out.

December 1933 : Left renal calculus with hydronephrosis was discovered and left nephrectomy performed. It was hoped that the wounds in the perineum would heal now that infection in the upper urinary tract was removed.

May 1934 : A vesical calculus was crushed and a urethral calculus removed.

September 1934 : An opening was found in the exposed anterior wall of the rectum.

Inguinal colostomy was performed because of the long delay in healing, the extensive wounds in the perineum, and the presence of a fistula in the rectum situated above the ano-rectal ring.

October 1934 : A plastic operation on the opening in the rectum was attempted and proved to be successful.

At this stage healing came to a standstill. The extensive granulating wound in the perineum exposed the apex of the prostate, the roof of the bulbous urethra

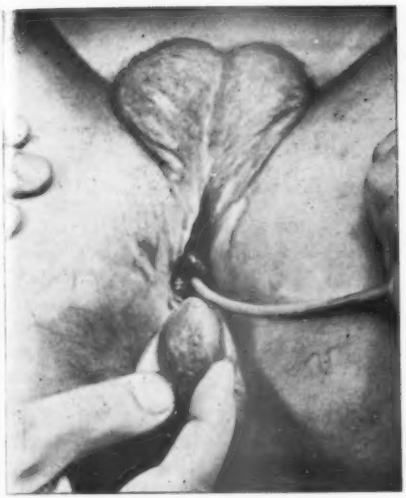


FIG. 1.—Extensive loss of perineal floor exposing apex of prostate and urethra.

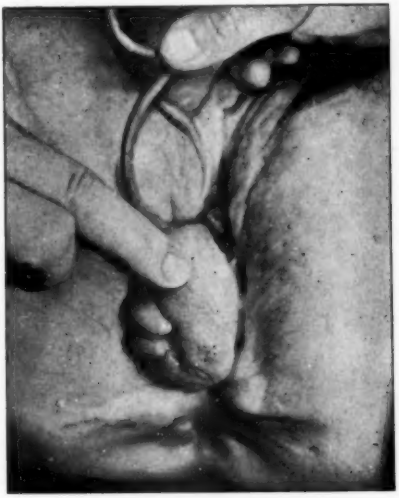


FIG. 2.—Œdematous anal canal projecting between the scarred ischiorectal fossæ.

FIG. 3.—Reconstruction of perineum showing gluteal region and flaps filling ischiorectal fossæ.

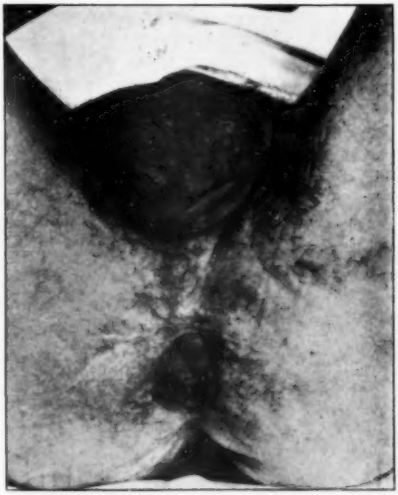


FIG. 4.—Reconstruction of urethra and anal canal.

and the anterior wall of the rectum and anal canal. The anus was isolated by an encircling wound. Its skin was swollen and œdematous for lymphatic drainage was destroyed, but sphincteric function was clinically unimpaired.

After two years of expectation one began to think healing would never occur because of lack of tissue and the œdematous isolated projecting anus.

Infection was absent except near the coccyx and this disappeared when the coccyx and part of the sacrum were removed.

Mr. A. H. McIndoe.—The patient was first seen by me at the Hospital for Tropical Diseases on March 5, 1936. The long and complicated history of continued infection with multiple operations had resulted in almost complete disorganization of the perineum, the remaining tissue being almost all scar. The apex of the prostate and 1½ in. of the urethra were exposed while loss of all circumferential attachment of the anal canal and lower rectum to the level of the prostate left it hanging as an œdematous mass between the scarred and deeply excavated ischiorectal fossæ. With a colostomy and suprapubic bladder drainage the patient's physical condition was miserable in the extreme, though his morale was excellent.

Estimation of the amount of tissue lost showed that while it might be possible to obtain local flaps for the formation of a urethral canal it would be necessary to import distant flaps to fill the ischiorectal fossæ and to reconstitute the perineal floor into which the detached anal canal could be reimplanted. Fortunately the tissue in the neighbourhood of the strip of urethral mucosa leading from the anterior urethra to the apex of the prostate was entirely scar, and contained no hair follicles to produce subsequent intra-urethral growth.

The operation was performed on February 6, 1936, under spinal anæsthesia. Lining flaps, chiefly scar tissue were turned in from each side of the urethral remains and sutured medially with interrupted catgut, turning the knots inside as for the Marion Duplay method of reconstruction in hypospadias. The protruding anus was then circumcised and stripped of all scar and œdematous fat until the longitudinal muscle-fibres were visible along with the remains of the external sphincter. This of course had lost its anterior and posterior attachments completely. The ischiorectal fossæ were cleaned of as much scar tissue as possible leaving a large excavation involving almost the entire perineum with the denuded anal canal and lower rectum dangling from its centre. This gap was then filled by turning medially two large gluteal rotation flaps measuring 7 in. by 6 in. based anteriorly and consisting of the full thickness of the skin and subcutaneous tissue down to the gluteus maximus. These were sufficiently thick to fill the central excavation so that no dead space existed above the urethral reconstruction or round the anal canal. Medial suture was then carried out leaving the anus appropriately placed between the two flaps. The lateral relaxation areas were left raw. Healing took place by first intention with the exception of one small urethral fistula just in front of the rectum. After three months when this had failed to close further investigation showed a urethral stone at the bottom of the sinus and a further collection of stones in the bladder. The urethral stone was extracted and the vesical calculi crushed and washed out via the suprapubic drain. Following this the fistula closed. Cautious efforts were then made to re-establish urethral bladder drainage by temporarily plugging the suprapubic opening, and gradually the patient was able to pass an excellent stream without discomfort and with perfect control.

At the end of eight months the epithelialized suprapubic hole was excised and the bladder closed. One month later the colostomy was closed and gastro-intestinal continuity re-established.

He left the hospital on January 8, 1937, eleven months after admission with a sound perineum, and no sign of anal œdema (See figs. 1–4). There was good

rectal and bladder control. Examination on September 8, 1938, showed him to be fit and well. Since his discharge the patient has been employed as an able seaman running foodstuffs into Spanish ports through the blockade.

FOUR SPECIMENS shown by LAWRENCE ABEL, F.R.C.S.

I.—Diverticulitis of Cæcum, Resembling Carcinoma.

G. W., male, aged 72.

History.—Four days colicky abdominal pain increasing in severity. Twenty-four hours absolute constipation. No vomiting. Treated for auricular fibrillation three months.

On examination.—Cyanosed; breathless; pulse 78, irregular. Firm, tender, fixed mass in right iliac fossa, size of grape-fruit; dull on percussion; abdomen distended; rectum loaded.

Treatment.—Five days' enemata; fomentations to abdomen; results of enemata contained melæna; acute obstruction overcome; mass reduced in size; high colon wash-outs given.

Investigation.—Barium enema X-ray: filling defect in cæcum, probably carcinoma. Diverticulitis in pelvic colon.

Operation (21.10.38).—Excision of last 10 in. of small intestine and colon as far as 4 in. distal to hepatic flexure. End-to-side anastomosis, small intestine to transverse colon.

II.—Abdomino-Perineal Excision of Rectum and Wertheim's Operation.

E. H., female, aged 36.

History.—Constipation six months. Rectovaginal fistula one month. Loss of weight, 3 st. in six months.

On examination.—Per rectum, large carcinoma of rectum 2 in. from anal orifice. Rectovaginal fistula.

Per vaginam, carcinoma invading vaginal wall up to posterior fornix.

Operation (16.4.37).—Combined abdomino-perineal excision of rectum and Wertheim's hysterectomy. Blood transfusion and continuous intravenous glucose-saline.

Pathology.—Columnar-celled adenocarcinoma.

Subsequent history.—18.6.38: Suprapubic intraperitoneal mass removed = adenocarcinoma. Subsequently improved with high-voltage therapy. 4.10.38: Readmitted for further high-voltage therapy. Still alive but with recurrence.

III.—Small Carcinoma of Pelvic Colon with Perforation of Enormous Growth into the Rectum.

B. C., female, aged 37.

History.—Four months' bleeding *per rectum*, with occasional diarrhœa and mucus, with attacks of constipation; loss of weight.

December 1937, laparotomy in the country. Condition diagnosed inoperable.

On examination.—Large carcinoma anterior rectal wall; fixed. *Per vaginam* no involvement of vagina.

Operations (25.2.38).—Laparotomy. Large pelvic mass involving pelvic colon and rectum; colon distended. Transverse colostomy instituted. 18.3.38: Abdomino-perineal excision. 10.6.38: Readmitted and transverse colostomy closed.

Pathology.—Large cauliflower tumour at first sight apparently based on anterior wall of rectum was found to communicate directly with a typical carcinomatous

ulcer of pelvic colon which encircles the lumen. Central ulceration through adherent loops of gut has occurred. Section shows columnar-celled adenocarcinoma. Five lymph nodes show no metastases.

Subsequent history.—Patient alive and well, November 1938.

IV.—Double Carcinoma of Pelvic Colon and Rectum.

E. S., female, aged 75.

History.—One year attacks of lower abdominal discomfort. Three months' blood and mucus *per rectum*.

On examination.—*Per rectum* sessile mass posterior rectal wall at pelvirectal junction. Sigmoidoscopy = suspicious polypoid growth. Biopsy: inconclusive.

Treatment.—Diathermy at time of sigmoidoscopy. Surgical diathermy to growth on account of age, general condition and ankylosis of right hip with 4 in. shortening. General condition improved.

Operation (28.10.38).—Abdomino-perineal excision of lower two-thirds of pelvic colon with growth and of rectum with growth. Blood transfusion and continuous intravenous glucose-saline forty-eight hours.

Subsequent history.—Patient out of bed on seventh day. Uninterrupted recovery.

A Case of Amœbic Ulceration of the Rectum and Anus.—W. B. Gabriel, M.S.

The patient B. P. was a man, aged 35, who was admitted into St. Mark's Hospital on April 12, 1938.

Previous history.—He had served in the Army and was abroad as a cook, from 1922–28, in India, Mesopotamia, Malta, and China. He was not ill during this time and denied having had dysentery.

Three years ago he developed an abscess in the anal region which ruptured and continued to discharge for two and a half years.

In January 1938 he was admitted into another hospital and was found to have a stricture just admitting the finger tip about 3 in. above the anus, with a friable ulceration below it which bled freely when touched: there was no induration suggesting a growth. A left iliac colostomy was performed, but in spite of irrigations the rectal discharge became worse, ulceration spread to the perineum and his general condition deteriorated.

State on admission.—The patient was extremely ill, emaciated and anæmic: evening temperature 101°, pulse 120. He presented an enormous ulcerating cavity in the anal region: the anal canal and anal muscles had completely disappeared, and a large area of gangrene of the skin and subcutaneous tissues was present at the posterior and anterior ends of the cavity. There was an area of ulceration and gangrene round the left iliac colostomy.

Investigation.—Biopsy fragments from the margins of the ulcerated area showed an intense infiltration of the tissues with inflammatory cells: the histology was not suggestive of tuberculous infection and there was no sign of neoplasm. The Kahn test and Wassermann reaction were negative. No tubercle bacilli were seen in three specimens of sputum. At first, no pathogenic protozoa or cysts were found on examination of the fæces, nor were amœbæ or cysts found in scrapings from the colostomy or anal ulcerations.

Course.—The patient was seen by my colleague, Mr. C. Naunton Morgan, who suggested the possibility of this being a case of amœbic ulceration. Treatment with emetine hydrochloride (gr. ½ b.d.) was begun on April 16, and four days later the patient already showed a dramatic improvement; his temperature was normal,

he felt better in himself and the large slough over the sacrum was beginning to separate.

On April 25, after nine days of emetine treatment, cysts of *Entamœba histolytica* were found in two specimens of fæces.

After completion of ten days' emetine treatment, the ulceration of the buttocks had cleaned up, and the sloughs almost entirely separated, leaving a smooth clean granulating surface. The ulceration round the colostomy had improved similarly.

Dr. Manson-Bahr confirmed the diagnosis of amœbic ulceration. On his advice, after a four days' interval, a ten days' course of emetine bismuth iodide (gr. 2 nocte)

FIG. 1.—On admission, April 1938.

FIG. 2.—After 8 days' anti-dysenteric treatment.

FIG. 3.—After Thiersch grafting five weeks after admission.

FIG. 4.—Ulceration completely healed, November 1938.

was given, together with injection of 2 oz. of 2½% Yatren into the distal colostomy opening daily (May 1 to 10). This completed the anti-dysenteric treatment.

Subsequently the exposed necrotic coccyx was removed under spinal anæsthesia, and the large granulating area in the perineum was covered with Thiersch grafts.

Present state (November 1938).—He is in excellent health and has put on about a stone in weight. The perineal ulceration is completely healed, the only discharge

FIG. 5.—Amœbic ulceration round colostomy.

coming from a small area of exposed rectal mucosa. His anal muscles are irretrievably lost and his colostomy must therefore be permanent.

Amœbic Ulceration of the Abdominal Wall.—C. NAUNTON MORGAN, F.R.C.S.

Although this case of Dr. Manson-Bahr's has been recorded elsewhere (*Tr. Roy. Soc. Trop. Med. and Hyg.*, 1938, **32**, 223), I am presenting it because of its comparative interest in the consideration of Mr. Gabriel's case of ulceration of the anus and perineum.

The patient was an ex-soldier aged 25. He had served in India for five years and was discharged from the army in January 1937. In March 1937 he was investigated for rectal hæmorrhage and sigmoidoscopy showed extensive ulceration which was thought to be carcinomatous—his general condition was poor. A left iliac colostomy was performed and soon after the operation, the wound became indurated and painful and spreading ulceration occurred from the edge of the wound. He was admitted into the Hospital for Tropical Diseases under Dr. Manson-Bahr in September 1937. Surrounding the colostomy there was an area of turgid red granulation tissue which itself was ulcerated. This area was approximately 5 in. in diameter. Its edges were raised and slightly everted, but were not hard. The ulceration was covered with offensive thick chocolate-coloured pus. There were tiny superficial ulcers only seen with a hand lens on the exposed loop of colon (fig. 1).

Sigmoidoscopy revealed extensive ulceration of the rectum. *Entamoebae histolytica* were obtained from the offensive discharge from the colostomy wound and from the proximal end of the colostomy. Amœbæ were also seen in the biopsy specimen from the edge of the ulcerated area on the abdomen.

After injection of 8 gr. of emetine the condition rapidly improved (fig. 2). The wound area was dressed with $2\frac{1}{2}\%$ quinoxyl.

Two months after admission the patient developed appendicitis with spreading peritonitis. Appendicectomy was performed and although the patient developed pneumonia and a pelvic abscess, he recovered and after four months' convalescence, the colostomy was closed.

This case, together with Mr. Gabriel's, is instructive in that when ulceration around a colostomy occurs, especially if it is associated with ulceration of the rectum,

FIG. 1.—H.T.D., September 1937.

FIG. 2.—After injection of 8 grains of emetine.

anal canal or peri-anal skin, the possibility of amœbic infection should be considered and even though *Entamoeba histolytica* cannot be found, a course of emetine should be given a trial if histological examination of the tissue excludes tuberculosis.

Intussusception caused by Malignant Growth.—MICHAEL SMYTH, M.Ch.

Female patient aged 75, complaining of intermittent abdominal pain for two and a half years.

Five days before operation, the pain got more severe and colicky in nature. She was seen by Dr. J. A. Flaherty, of Beckenham, who discovered a large mobile tumour in the right side of the abdomen.

X-ray diagnosis.—polyp, diverticula, or possibly chronic intussusception of the large intestine (figs. 1 and 2).

Operation (10.9.38).—The cæcum, appendix and a portion of the small intestine had intussuscepted, and together with the tumour formed a large swelling occupying the position of the ascending colon and the hepatic flexure. There was no evidence of obstruction, so the operation was done in one stage. The tumour was easily mobilized and presented no difficulty in removal. Resection included the lower 6 in. of the visible portion of the small intestine and the colon as far as the middle of the transverse colon. Closure of both ends and lateral anastomosis performed.

Recovery uninterrupted.

Report on tumour (C. E. Dukes): Gross characters: The specimen consisted of a large intussusception of the small intestine into the large intestine (fig. 3). Dissection revealed a large fungating growth forming the apex of the intussusception

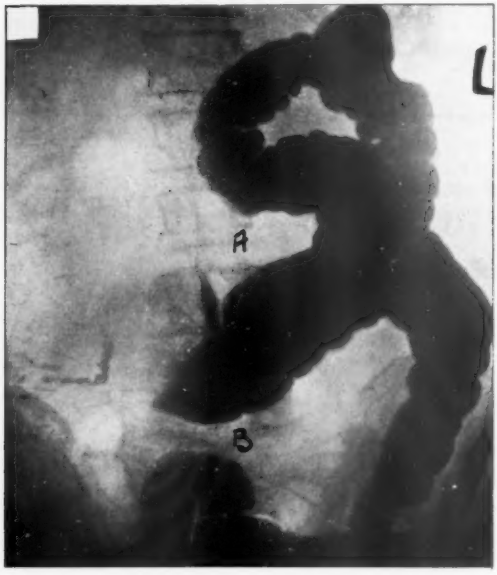


FIG. 1.—The barium enema runs easily to the proximal third of the transverse colon where it begins at A and B to outline a mass in the gut.

FIG. 2.—The mass (AB) is outlined by the barium meal.

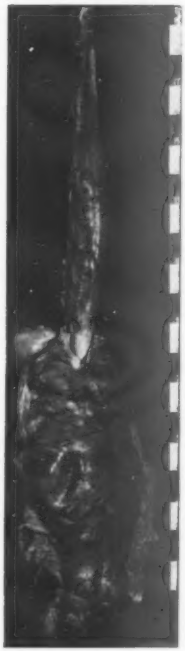


FIG. 3.

FIG. 4.

(fig. 4). Microscopic structure: The growth at the apex of the intussusception is a colloid carcinoma. There was no sign of venous or lymphatic spread. (Six glands examined.)

Early Carcinoma of the Rectum.—RONALD W. RAVEN, F.R.C.S.

R. S., female, aged 62. Cook. Attended the Gordon Hospital complaining of bleeding *per rectum*.

History.—For several weeks patient has had slight bleeding *per rectum*. One week ago attack of severe bleeding *per rectum*. No pain. No diarrhœa. No discharge *per rectum*. Bowels open regularly with aperients.

On examination.—General condition fair. Not markedly pale. Chest: Heart and lungs—no abnormality. Abdomen: No abnormality. Anus: No abnormality. Rectum: Digital examination—no abnormality. Proctoscopy—no hæmorrhoids. Sigmoidoscopy—At 10 cm. from the anal orifice on the posterior wall of the rectum was a small ulcer with a proliferative edge. Bleeding occurred when it was touched. Biopsy performed.

Operation.—(1) Exploratory laparotomy—no metastases present. Left inguinal colostomy established. (2) Perineal excision of rectum.

Result.—Patient made a good recovery from the operation.

Specimen.—The specimen is that of a rectum with a small carcinomatous ulcer with a proliferating edge size ¼ in. diameter. Microscopical examination : Vertical sections passing through the centre of the small tumour show portions of a columnar-celled adenocarcinoma invading the submucous layer. A small group of the tumour cells surrounded by small round cells evidently representing the base of a crypt in

Early carcinoma of the rectum. (Site of ulcer indicated by arrow.)

which the epithelium has undergone malignant change is seen also within the upper limit of the circular muscle layer. A small abscess is present at the site of biopsy. Only two lymph nodes were found and both are free from evidence of carcinomatous invasion.

Comment.—This specimen is of interest showing an extremely early carcinoma of the rectum and the early stage in the development of primary carcinoma in the rectum.

A Case of Gas Gangrene of the Rectum following a Local Removal of Polypoid Growth.—E. J. Radley Smith, M.S. (introduced by E. G. Muir, M.S.).

The patient was a woman aged 64, of good health and rather slight physique. She complained of blood-stained discharge *per rectum* for five years. When the bowels were open, a mass prolapsed through the anus. She had no pain, no constipation and no other symptoms. The only abnormality was that a mass could be felt on rectal examination on the posterior wall of the rectum. This mass was freely mobile and could be drawn down through the anus quite easily. It appeared to be a simple tumour of the mucous membrane.

Diagnosis of a simple tumour was confirmed by a sigmoidoscopy. On 3.11.38 under general anæsthesia the anus was dilated and the tumour pulled down through it. It was found that the lower part was pedunculated but the upper part was sessile. The tumour appeared to involve the mucosa only and was easily moved over the muscle coats. Local excision was performed and the incision in the mucosa was sewn up. At the end of the operation, 12 noon on 3.11.38, the patient was perfectly fit. At 6 a.m. the next morning she was quite comfortable ; the pulse was only 90. At 7 o'clock, the pulse had risen to 120 but there was no hæmorrhage *per rectum* although a drain had been passed through the anus. Her condition was fair. At 8 a.m. she was very much worse and she complained of severe abdominal pain. The abdomen was very distended and rigid. On rectal examination the absence of bleeding was confirmed, but a foul-smelling discharge was seen and crepitus was felt in the rectal wall. This crepitus was exactly like that felt in surgical emphysema. The pulse had now risen to 140 and anti-gas gangrene serum was given. At 9 a.m. she was delirious with an almost imperceptible pulse. Ether was administered and the stitches removed from the incision in the rectal wall. The post-rectal space was opened and drained and the rectum itself was irrigated with peroxide. While this was being done she died. Her death occurred before 10 a.m. on the 4th, namely under twenty-two hours from the first operation.

A post-mortem examination was carried out the same day. The peritoneal cavity contained purulent foul fluid and all the abdominal organs and extraperitoneal tissues contained bubbles of gas.

Comment.—This case has been reported because of the rarity of gas gangrene of the rectum following a comparatively trivial operation. In this case the operation was a simple one performed through the anus. She did not suffer from any loss of blood and was not shocked. The rectum appeared to be quite clean at the time of the operation. There was certainly no sloughing of tissues and no dead or necrotic muscle in which organisms would find a favourable site for their growth. Her death was extremely rapid and the toxæmia seemed to be quite overwhelming. In twenty hours from the operation she was hopelessly ill and she died in under twenty-two hours. Incidently, no prophylactic anti-gas gangrene serum had been given. The fluid obtained from the peritoneal cavity grew *B. welchii* and anaerobic streptococci. The catgut used at the first operation has been examined but nothing has grown.

Three Specimens shown by E. G. Muir, M.S.

I.—Terminal Ileitis.

The patient, a doctor aged 30, had known since he was a student some six years ago that he had a small lump in the right iliac fossa. He had never suffered from any abdominal illness as a child. For the past two years the lump had slowly increased in size and was sometimes uncomfortable. He was first seen on October 17, 1938, when he had symptoms of a subacute intestinal obstruction. A firm mass was

easily palpable iu the right iliac fossa. X-rays showed obstruction at ileocæcal region with a thin streak of barium in the terminal ileum.

22.10.38: Excision of terminal ileum, cæcum and ascending colon. A small abscess was present behind the cæcum. Uneventful convalescence.

Histology: Chronic inflammatory changes in and around the ileocæcal junction. Acute inflammatory changes in wall of abscess. No evidence of tubercle in bowel or in glands.

II.—Prickle-celled Carcinoma of Rectum.

Removed by perineo-abdominal resection from a man aged 34. He had experienced some rectal discomfort and constipation for a fortnight.

In the specimen shown at the meeting, the growth was spreading around the three terminal branches of the superior hæmorrhoidal artery. Three glands at the point of ligature of the inferior mesenteric artery were histologically free from secondary deposits.

Histology.—Prickle-celled carcinoma.

III.—? Lymphoma of Ileum.

The patient, a boy aged 8, was seen with an attack of colicky abdominal pain and signs suggesting an acute appendix. There was a history of similar attacks during the past year. Operation through a grid-iron incision showed a normal appendix but there was a great thickening of the *mucosa* in the last 6 in. of ileum. It felt on palpation as if it contained a mass of polypi. Similar changes, though less marked were present in the last 2 ft. of the small bowel. Many large glands were present in the ileocæcal angle, some over an inch diameter. It was thought to be a lympho-sarcoma and the terminal two feet of ileum, the cæcum and ascending colon were resected. The child stood the operation well and left hospital in three weeks.

Blood-count normal. X-ray of chest normal.

It is now fifteen months since the operation and the child remains in good health.

Histology.—? Lymphoma. ? diagnosis.

Proceedings of the Royal Society of Medicine Vol. XXXII
911

Section of Obstetrics and Gynæcology

President—ALECK W. BOURNE, F.R.C.S.

[*March* 17, 1939]

Serum and Vaccine Therapy in Combination with Sulphanilamide or M and B 693

By ALEXANDER FLEMING, F.R.C.S.

In the past many chemicals have been recommended for intravenous injection or for introduction into the body in other ways with the object of directly killing infecting bacteria. With the exception of the salvarsan group they have been found wanting, although sometimes one and sometimes another has had, for a time, a certain vogue.

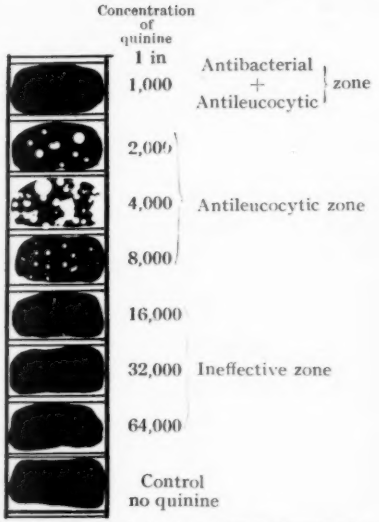
Let us see what happens when the antibacterial action of these chemicals is tested in human blood; and we may take as an example quinine, which has been recommended as an intravenous injection for the treatment of puerperal septicæmia due to *Streptococcus pyogenes*. If human defibrinated blood infected with a suitable dose of *Streptococcus pyogenes* is mixed with serial dilutions of quinine and incubated in slide cells the resulting growth is as illustrated in fig. 1.

In the blood without quinine there is no growth as the phagocytes of the blood can deal with all of the infecting bacteria. In the weakest concentrations of quinine there is the same result, but as the concentration of quinine increases so hæmolytic colonies of streptococci appear until when there is a concentration of 1 : 4,000 in the blood all the streptococci implanted in the blood grow out. This is due to the fact that chemicals like quinine have a more poisonous action on leucocytes than they have on streptococci. Had it been possible to administer quinine in a dose sufficient to produce in the blood a concentration of 1 : 4,000 the result would have been serious as the blood would have lost all its anti-streptococcal power and have become a first-class culture medium for the streptococcus. The dose recommended was, however, 2 gr., which if introduced into the blood-stream could not give a concentration of more than 1 : 40,000. It will be seen by referring to fig. 1 that this concentration is well off the scale, and would have no effect on the bacteria or on the leucocytes.

When sulphanilamide was introduced I was interested to see whether it had any such antileucocytic action. The test was made in exactly the same way except that the indicator organism was a hæmolytic enterococcus—a microbe which is quite insensitive to sulphanilamide. The result obtained is shown in fig. 2.

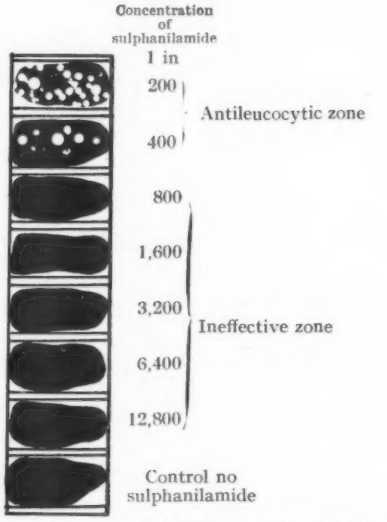
This shows that there is no antileucocytic effect until a concentration of sulphanilamide of 1 : 400 is reached—a concentration far greater than can be attained in the blood therapeutically. More recently similar experiments were made with M & B 693 and it was likewise found that this drug had no antileucocytic effect in any significant concentration.

A very different picture is obtained when the antibacterial power of sulphanilamide or M & B 693 is tested on a sensitive microbe such as the *Streptococcus pyogenes*. If such a test is made in exactly the same way as is illustrated in fig. 1 except that sulphanilamide or M & B 693 is used instead of quinine a result is obtained which is shown in fig. 3.



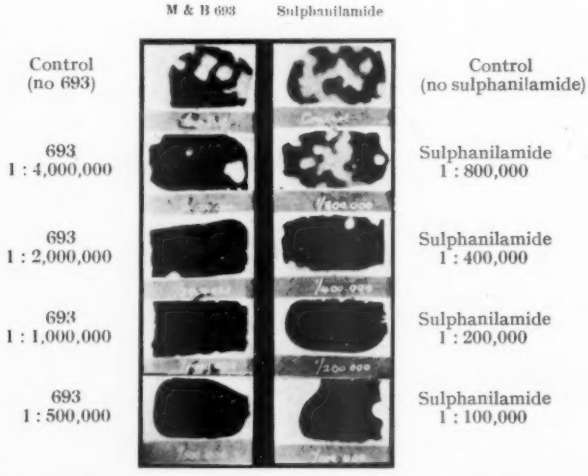
The white spots indicate areas of hæmolysis due to the growth of *Streptococcus pyogenes*.

FIG. 1.—Effect of quinine on the growth of *Streptococcus pyogenes* in human blood.



The white spots indicate areas of hæmolysis due to the growth of hæmolytic enterococcus.

FIG. 2.—Effect of sulphanilamide on a hæmolytic enterococcus in human blood.



The light patches represent areas of hæmolysis caused by growth of the streptococci.
M & B 693 appears to be ten times stronger than sulphanilamide on a typical Group A hæmolytic streptococcus.

FIG. 3.—Comparison of the antistreptococcal power of sulphanilamide and 693.

Here it can be seen that in human blood some antibacterial action is manifest in concentrations of the drugs far weaker than can be obtained by their oral administration. It can also be seen that on *Streptococcus pyogenes* M & B 693 is something like ten times as potent as sulphanilamide. (Complete inhibition of growth with 1 : 1,000,000 of M & B 693 and 1 : 100,000 of sulphanilamide.)

Leaving aside the question of toxicity of such drugs a simple test of this nature gives very valuable information ; a result such as is shown in fig. 3 gives a very strong indication that therapeutic success would follow the administration of these drugs.

A criticism might be offered that it is easy to say this now that sulphanilamide and 693 have proved themselves therapeutically successful, but I first published this method of testing antibacterial chemicals in 1924 and it has appeared since in various publications including the *Proceedings* of this Society.

The exact mode of action of drugs like sulphanilamide or M & B 693 is still unsettled, but it is generally accepted that the action is on the infecting bacteria and not on the host ; and that it is bacteriostatic rather than bactericidal. The chief result of the drug on the bacteria is some interference with their growth, and this is well brought out in two experiments which I have already published (1938).

Demonstration of the Bacteriostatic Action of M & B 693 on Pneumococci

Human blood was deprived of its leucocytes by passing it through a tight cotton-wool filter. Such deleucocyted blood has no antibacterial action on pneumococci. This blood was infected with a suitable dilution of a pneumococcus culture and was mixed in equal volumes with serial dilutions of M & B 693 in normal saline. The mixtures were incubated in slide cells for twenty-four hours, when the resultant growth was noted. The results obtained are shown in Table I.

TABLE I.—INFLUENCE OF M AND B 693 ON PNEUMOCOCCUS IN DELEUCOCYTED BLOOD.

Concentration of M and B 693	Number of colonies developing from an inoculum of 100 cocci
0 (control)	106
1 : 500,000	114
1 : 250,000	118 small
1 : 128,000	108 smaller
1 : 64,000	102 minute
1 : 32,000	90 minute
1 : 16,000	107 minute
1 : 8,000	94 minute

This shows that the drug in a concentration of 1 : 8,000, which is about the maximum which can be obtained in the body therapeutically, has no bactericidal action on pneumococci, but there is a marked inhibition of growth as shown by the very small size of the colonies in all concentrations greater than 1 : 250,000.

With a more sensitive microbe such as the *Streptococcus pyogenes* inhibition of growth may be complete, and even after prolonged incubation no colonies appear but the cocci may still survive as is shown in the next experiment.

Serum from a patient who was taking M & B 693 in large doses was infected with a sensitive *Streptococcus pyogenes* so that 25 c.mm. of the serum contained 115 cocci. This infected serum was incubated in 25 c.mm. volumes in capillary tubes, and at intervals the whole of the contents of one tube were planted into glucose broth to ascertain whether the streptococci had been killed. The result obtained was as follows :—

Planted in glucose broth after { 18 hours / 24 hours / 48 hours } growth

It was estimated chemically that this sample of serum contained M & B 693 in a concentration of 1 : 10,000, but it is clear that 25 c.mm. could not kill 115 streptococci in two days.

As these drugs do not actually kill the infecting bacteria something else must do it to account for the striking success which has followed their use in experimental infection of animals and in medical practice. That something is the natural defensive mechanism of the body which, while it might be powerless against a rapidly growing streptococcal or pneumococcal infection, can cope with the infection when the growth of the bacteria is interfered with by the drug.

Even with the most sensitive organisms these drugs do not effect a cure in every case, and I am bringing forward evidence to show that the results obtained by increasing the power of the defensive mechanism, in other words, by increasing the immunity, are, in combination with these drugs, far superior to immunotherapy or chemotherapy alone. The immunity can be increased specifically by vaccine and serums and non-specificially by a great variety of measures.

Passive Immunity in Association with Chemotherapy

Several workers have shown that specific antiserums enhance the apparent effect of sulphanilamide treatment.

De and Basu (1938), working with staphylococcus, used a combination of an antitoxic and an antibacterial serum, and showed that mice infected with staphylococci could be saved by the administration of these serums combined with sulphanilamide treatment although neither the serum nor the sulphanilamide treatment saved the animals.

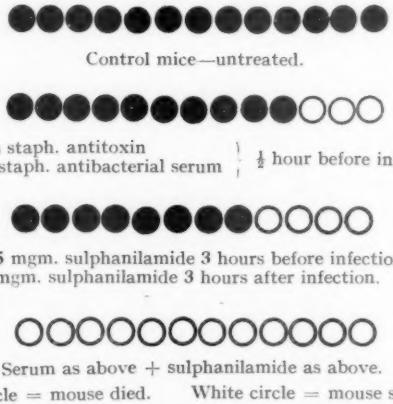

Control mice—untreated.
50 units staph. antitoxin
0·5 c.c. staph. antibacterial serum
½ hour before infection
3·5 mgm. sulphanilamide 3 hours before infection.
4 mgm. sulphanilamide 3 hours after infection.
Serum as above + sulphanilamide as above.
(Black circle = mouse died. White circle = mouse survived.)

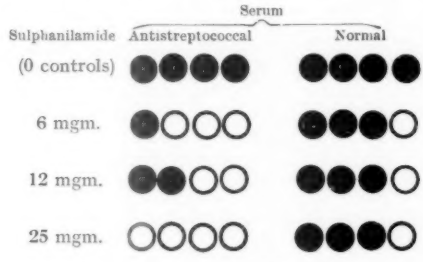
FIG. 4.—Combined action of antistaphylococcal serum and sulphanilamide. Adapted from De and Basu.

Fig. 4, which is adapted from the figures given by De and Basu, shows graphically the results which they obtained. All the controls died, all the animals having the combined treatment lived, and only a few survived that had serum or chemotherapy alone.

Of greater interest possibly are the results published by Loewenthal (1939) on the synergic action of antistreptococcal serum and sulphanilamide in experimental streptococcal infections in mice.

Loewenthal chose a dose of serum which he knew would not protect the mice against his experimental infection, and likewise a dose of sulphanilamide too small

to be completely effective. In one series of experiments he gave the serum eighteen hours before the animals were infected and then immediately after infection the mice received orally a single dose of sulphanilamide. I have set forth graphically in fig. 5



(Black circle = mouse died. White circle = mouse survived.)

FIG. 5.—Combined serum and sulphanilamide treatment.
Serum given 18 hours before infection.
Sulphanilamide given immediately after infection.
(Adapted from Loewenthal.)

the results which he obtained, which show clearly that even with a very small dose of sulphanilamide a greater number of the serum-treated animals survived ; and with a dose of 25 mgm. all the mice recovered although in the control series only one out of four survived.

In a second series the mice were infected with streptococci and nothing was done for eighteen hours, by which time the mice were very ill.

Then the mice were divided into four batches, which were treated as follows :—

(1) 0·5 c.c. of normal rabbit serum.
(2) 0·5 c.c. of antistreptococcal serum (rabbit).
(3) 0·5 c.c. of normal rabbit serum + 20 mgm. of sulphanilamide.
(4) 0·5 c.c. of antistreptococcal serum + 20 mgm. of sulphanilamide.

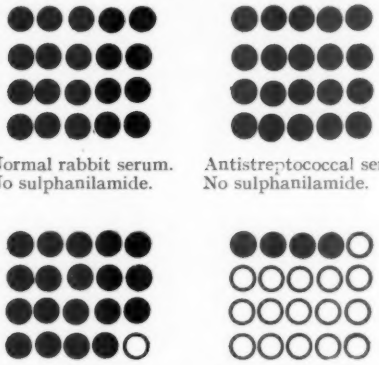
His results I have adapted into fig. 6, which shows at a glance that the only treatment which was effective was the combination of antistreptococcal serum and sulphanilamide.

There is as yet no published work on the combination of serum therapy and M & B 693, but I have shown *in vitro* that the addition of antipneumococcal serum greatly enhances the antipneumococcal power of a mixture of human blood and M & B 693.

Normal human defibrinated blood was infected with pneumococcus Type 1, and 25 c.mm. of this was mixed with 25 c.mm. of dilutions of M & B 693 and 10 c.mm. of Type 1 antipneumococcal serum or saline. These mixtures were placed in slide cells in the incubator and after twenty-four hours the number of colonies was enumerated.

TABLE II.—INFLUENCE OF M & B 693 ON PNEUMOCOCCI (TYPE 1) IN HUMAN BLOOD WITH AND WITHOUT IMMUNE SERUM.

25 c.mm.	+	25 c.mm.	+	10 c.mm.	No. of colonies
Blood		Saline		Saline	∞
Blood		Saline		Immune serum	360
Blood		M & B 693 1 : 16,000		Saline	∞
Blood		M & B 693 1 : 32,000		Immune serum	0
Deleucocyted blood		M & B 693 1 : 16,000		Immune serum	∞



(Black circle = mouse died. White circle = mouse survived.)

FIG. 6.—Combined serum and sulphanilamide treatment of mice infected 18 hours previously with a hæmolytic streptococcus.
(Adapted from Loewenthal.)

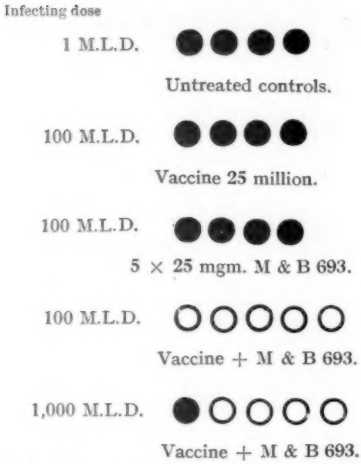
It is clear from this that the combination of immune serum and M & B 693 was the only one effective in preventing the growth of pneumococci in human blood, and there is little doubt that the same combination will be most effective in the treatment of pneumonia in man. You will see, however, that when the leucocytes are removed from the blood the combination of M & B 693 and immune serum is without effect.

Vaccine Therapy in Association with Chemotherapy

We have seen that passive immunity by means of serum has a striking effect when induced in association with treatment by sulphanilamide or M & B 693. In passive immunity ready formed antibodies are introduced into the infected animal, but there is no reason why the animal should not make its own antibodies in response to a vaccine, and it is probable that, if there is time, the concentration of antibodies in the blood of the infected animal immunized with a vaccine would be much greater than it would be if a therapeutic dose of serum was administered, for this dose is of necessity of small bulk compared with the amount of blood in the body and would therefore be greatly diluted. Maclean, Rogers and myself, therefore, made experiments to ascertain whether by means of a single dose of vaccine sufficient immunity could be developed in an animal to make any difference to the results obtained when the animals were infected and then treated with M & B 693.

Mice received a single dose of 25 million pneumococcus vaccine, and then after six days they were infected with 100 minimum lethal doses of a virulent pneumococcus culture. (From previous experiments it was known that with that dose treatment with five daily doses of 25 mgm. of M & B 693 failed to save any of the mice.) Then some of the mice were treated with five daily doses of M & B 693 and some were not, and at the same time control unvaccinated mice were infected and of these some were treated in the same way with M & B 693 and some were not.

The results we obtained are shown in fig. 7, and it is clear from this diagram that whereas the vaccine or the M & B 693 failed to save any of the mice infected with 100 minimum lethal doses of pneumococci the mice which had been injected with the vaccine had developed sufficient immunity that when they were infected with 100 minimum lethal doses and treated with M & B 693 they all recovered, and even



(Black circle = mouse died. White circle = mouse survived.)

FIG. 7.—Synergic action of pneumococcal vaccine and M & B 693.
(Adapted from Maclean, Rogers, and Fleming.)

when 1,000 minimum lethal doses of pneumococci were given five out of six mice recovered. From this experiment there is no question as to the synergic action of vaccine therapy and M & B 693 treatment.

To confirm this a second experiment was done in the same way except that the dose of vaccine was 100 million instead of 25 million. The results obtained are shown in fig. 8, and it will be seen that they are essentially the same as in the last experiment.

Further confirmatory tests were done in rabbits, and here the infection of pneumococcus was made intradermally instead of intraperitoneally, as in the case of the mice. The rabbits received a single dose of vaccine six days before they were infected. The control rabbit and the one which received the vaccine, but no M & B 693, died

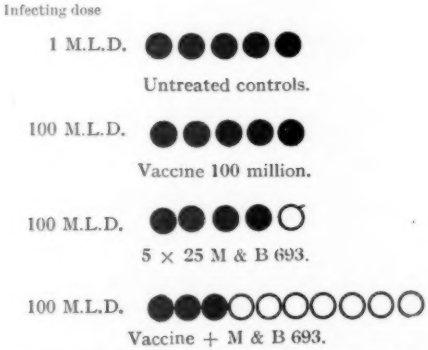


FIG. 8.—Synergic action of pneumococcal vaccine and M & B 693.
(Adapted from Maclean, Rogers, and Fleming.)

with a pneumococcal septicæmia. The unvaccinated rabbit treated with M & B 693 recovered, but had a very serious illness for four days, during which time pneumococci could be recovered from the blood. The vaccinated rabbit treated with M & B 693 also recovered, but had only a trifling illness, and blood cultures taken at intervals over four days remained sterile. The temperature charts of these last two rabbits are shown in fig. 9, and these charts illustrate very well the difference which a single dose of vaccine made in the severity of the illness in animals infected with the same number of the same microbes and both treated in exactly the same manner with M & B 693.

There is a certain amount of clinical confirmation of these results which we have obtained in animals. Cokkinnis and McElligott (1938), in a large series of observations

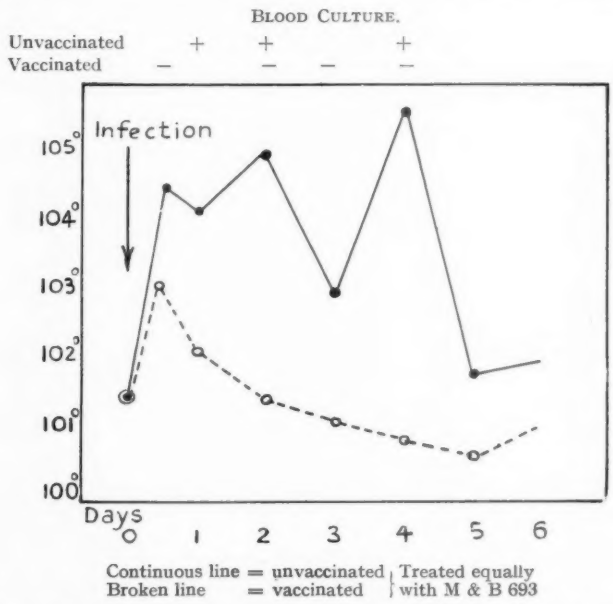


Fig. 9.—Temperature charts of vaccinated and unvaccinated rabbits treated with M & B 693.

(Adapted from Maclean, Rogers, and Fleming.)

on patients suffering from gonococcal infections, have found that better results were obtained when sulphanilamide treatment was withheld for eight to ten days after the onset of the infection. By doing this they obtained a more rapid " cure " and a freedom from relapses. Their explanation of this is " that it takes that much time for the body to acquire enough immunity to dispose of the organisms arrested by sulphanilamide ". They give an interesting table which I have condensed, showing the results obtained in patients treated during the first week of the disease. These patients consisted of over 100 who had never had the disease before, and about half that number who had suffered previously, and in most of whom the complement-fixation test was positive, indicating some degree of increased immunity to the gonococcus. You will see from Table III that much better results were obtained in the second group.

TABLE III.—ANALYSIS OF CASES TREATED IN THE FIRST WEEK OF GONORRHŒA. (ADAPTED FROM COKKINNIS AND MCELLIGOTT.)

	No. of cases	Good result in one course	Relapsed
First attack	103	39 (38%)	61(59%)
Not first attack ..	51	31 (61%)	17(33%)

First group complement-fixation test negative in all.
Second group complement-fixation test positive in 42.

Lyons and Mangiaracine (1938) have put forward evidence that the state of immunity of the patient plays a large part in the success or failure of sulphanilamide treatment. They divide acute hæmolytic streptococcal infections into three classes:—

(1) The patients have antibacterial antibody to their organisms at the time treatment is started.

(2) No antibacterial antibody is present and there is a negative blood culture with beginning localization of their infection by the process of inflammatory fixation.

(3) There is a bacteriæmia with no antibacterial antibody.

In this last class they state that sulphanilamide therapy has failed to sterilize the blood-stream.

More recently Ordman (1939) has made some interesting observations on the results which he, in conjunction with Agranat and Dreosti, have obtained in the treatment of pneumonia with M & B 693 in S. Africa. Certain sections of the native mining population are inoculated prophylactically with pneumococcus vaccine, and Ordman has compared the results in such communities with other similar uninoculated communities. The Randfontein Estates furnished a group wholly inoculated while the patients entering the Non-European Hospital in Johannesburg were not inoculated. Ordman has compared the duration of pyrexia in these two groups, each of which was divided approximately equally into a control group and a group treated with M & B 693. His comparisons are shown in Table IV, from which it is

TABLE IV.—COMPARISON OF DURATION OF PYREXIA IN PROPHYLACTICALLY INOCULATED AND UNINOCULATED AFRICAN NATIVES SUFFERING FROM PNEUMONIA.

	Percentage of cases showing a normal temperature within 4 days of admission to hospital	
	Control (No. 693)	Treated with 693
Inoculated	12·6	92·9
Not inoculated	38·5	60·0

Agranat,' Dreosti, and Ordman.

clear that the duration of pyrexia in the patients who had been prophylactically inoculated with pneumococcal vaccine was, in combination with 693 treatment, much less than in the group which had not been so inoculated.

This clinical evidence is not, of course, conclusive, but it is very significant when taken in conjunction with the experimental evidence which I have given above.

I will conclude by summing up the new chemotherapy by sulphanilamide and M & B 693. These drugs act on certain sensitive bacteria in some way so that their reproduction is retarded or abolished. When this has happened the natural defensive mechanism of the body completes the task by destroying the bacteria. The result, therefore, which will be obtained in any particular case will depend on two things: firstly the sensitiveness of the infecting organism to the drug, and secondly the state of immunity of the patient. I have attempted in Table V to set forth shortly the expectation of a good result in various conditions of immunity and sensitivity of the organism.

TABLE V.

State of immunity	Sensitivity of infecting organism to drug	Expectation of good result
High	High	Certain
High	Low	Probable
High	Nil	Uncertain
Medium	*High*	*Probable*
Medium	*Low*	*Unlikely*
Medium	*Nil*	*Poor*
Low	High	Uncertain
Low	Low	Very unlikely
Low	Nil	Nil

The ordinary individual may, as regards the common pyogenic organisms, be regarded as having a medium degree of immunity which can be increased actively or passively.

In an acute case one cannot tell whether the infecting organism is one which is very sensitive to these drugs so that, if the patient is to have the best chance, every endeavour should be made at the same time that the drug is administered to increase the immunity by vaccines or serums or by non-specific measures.

Serums are only obtainable for certain infections, but vaccines can be obtained, or can readily be prepared, for practically every acute bacterial infection.

REFERENCES

AGRANAT, A. L., DREOSTI, A. O., and ORDMAN, D. (1939), *Lancet* (i), 380.
COKKINNIS, A. J., and MCELLIGOTT, G. L. M. (1938), *ibid.* (ii), 355.
DE, S. P., and BASU, U. P. (1938), *Brit. M. J.* (ii), 564.
FLEMING, A. (1924), *Proc. Roy. Soc., London, s.B.*, **96**, 171; Id. (1931), *Proc. Roy. Soc. Med.*, **24**, 46.
Id. (1938), *Lancet* (ii), 74.
Id. (1938), *ibid.* (ii), 564.
LOEWENTHAL, H. (1939), *ibid* (i), 197.
LYONS, C., and MANGIARACINE, A. (1938), *Ann. Surg.*, **108**, 813.
MACLEAN, I. H., ROGERS, K. B., and FLEMING, A. (1939), *Lancet* (i) 562.

Professor F. J. BROWNE said he had always understood that a patient who was suffering from an acute infection such as puerperal septicæmia was being sufficiently vaccinated by the infecting organism and therefore did not require any further vaccine.

The Effects of Injection of Pituitary Extract Immediately after Delivery

By BERNARD L. WILLIAMS, F.R.C.S.Eng.

AT a recent examination discussion arose between the examiners as to whether untoward occurrences resulted from the injection of pituitary extract immediately following the birth of the child, and also as to whether there was any tangible advantage to be gained by this procedure. This experiment was therefore undertaken at the suggestion of Mr. James Wyatt, who was one of the examiners concerned.

The *objects* were as follows :—

(1) To note the incidence of any complication, such as contraction ring, that would in any way be attributable to the use of pituitary extract.

(2) As regards hæmorrhage, to note :—

(*a*) Incidence of post-partum hæmorrhage. (Post-partum hæmorrhage was said to occur when the total loss exceeded 20 oz.)

(*b*) Whether the average loss was affected by the injection of pituitary extract.

(3) To note whether the third stage was shortened.

Fifty normal primiparæ were taken, i.e. cases at or within two weeks of term where no abnormality (such as malpresentation, disproportion, or toxæmia) had been discovered in pregnancy, and in whom labour was uncomplicated and did not exceed forty-eight hours in duration.

Fifty similar cases were selected as controls.

The preparation used throughout was posterior lobe extract. A dose of 5 units was used in each case, i.e. 0·5 c.c. of the preparation. The injection was given intramuscularly immediately after the birth of the child.

The third stage was conducted as follows: Following ligation of the cord and separation of the child the patient was turned on to her back. The student or pupil-midwife conducting the delivery then placed a hand above the fundus and was instructed not to interfere with the uterus in any way, but to report at once any alteration in shape, size, or consistency. When the placenta was thought to have left the uterus as evidenced by the rising up and alteration in shape of the latter or by elongation of the cord, an effort was made to expel the placenta from the vagina by pressure on the fundus of the contracting uterus.

The duration of the third stage was noted in all cases.

The loss was collected in two receivers, one being used until the birth of the placenta, the other after. It must be admitted that this method was a very rough and ready one, and that in a few of the cases blood was unavoidably spilled into the bed, and the quantity thus lost was guessed at. Also it must be noted that the residual liquor amnii in the uterus may constitute a further source of error in estimating the blood lost.

The figures therefore must be taken as very approximate, but the same sources of error, it must be remembered, applied to the control series as well.

TABLE OF RESULTS.

Number of normal primiparæ.	
Given pituitary extract	50
Controls	50
Average loss in third stage.	
(*a*) Including cases of post-partum hæmorrhage	
Given pituitary extract	8·7 oz.
Controls	8·3 oz.
(*b*) Excluding cases of post-partum hæmorrhage	
Given pituitary extract	5·5 oz.
Controls	7·5 oz.
Incidence of post-partum hæmorrhage	
Given pituitary extract	5 cases
Controls	2 cases
Average duration of third stage	
Given pituitary extract	8·3 minutes
Controls	13·5 minutes

REVIEW OF INDIVIDUAL CASES OF POST-PARTUM HÆMORRHAGE

A.—Following Pituitary Extract

(1) Mrs. A., aged 21. Duration of labour: First stage 5 hours; second stage 1 hour.

The placenta remained *in utero* for a total duration of one hour. There was a steady trickle of blood and after half an hour two unsuccessful attempts at expression were made by Credé's method. Gas and air analgesia was given for these. Further loss resulted, bringing the total up to 15 oz. A general anæsthetic (gas, oxygen, and ether) was then given, and a third unsuccessful attempt at expression made. The loss became brisk and it was decided to remove the placenta manually. A portion of the placenta was felt protruding through the cervix and higher up an obstruction to the hand was encountered. A capsule of amyl nitrite was broken on to a swab and the swab placed in the mask. The obstruction was felt to relax and the hand was then passed up easily into the uterus, where the placenta was found to be adherent over the right upper quadrant. It was separated with the fingers and withdrawn complete.

The total loss was 70 oz.

The patient was given a blood transfusion and made an uninterrupted recovery.

(2) Mrs. P., aged 20. Duration of labour: First stage 18 hours; second stage 1¼ hours.

The third stage was uneventful.

The placenta and membranes were expelled complete after eight minutes. The total loss up to this point was 15 oz.

All loss had ceased and the uterus was firmly retracted when the patient was returned to the ward.

Half an hour later she complained that the bed was wet, and she was found to be in a pool of bright blood. The uterus was atonic and full of clots. It was massaged, a contraction obtained, and the contents expressed. Oxytocics (ergometrine and a further 5 units of pituitary extract) were given. but the uterus remained atonic and the bleeding continued. The abdominal wall was fortunately very thin and flabby, and a form of " monomanual " compression was performed, a hand being placed behind the uterus and pressing it down against the symphysis pubis for half an hour. This measure was effective in stopping the bleeding. The patient responded well to treatment for hæmorrhage and recovery was uneventful.

(3) Mrs. G., aged 22. Duration of labour: First stage 6 hours; second stage 2 hours.

The loss prior to expulsion of the placenta totalled 10 oz., that after, 15 oz.

The uterus in this case remained soft and atonic after the birth of the placenta. A slow trickle of blood went on for a quarter of an hour. Ergometrine was injected and the uterus massaged, whereupon tone returned and the bleeding ceased. Recovery was good.

(4) Mrs. E., aged 31. Duration of labour: Total 36 hours.

Throughout the third stage the uterus was unusually firm. There was a steady loss before the placenta had left the uterus, amounting to 15 oz. Credé's expression, under gas and air analgesia, was unsuccessful, so a more vigorous expression was done under full anæsthesia; this was successful, but was accompanied by a considerable gush of blood. The uterus then retracted firmly and there was no further loss for fifteen minutes, after which the uterus relaxed and 10 oz more were lost. Oxytocics (ergometrine and pituitrin) were given with good effect.

This case is of especial interest when compared with Case 2 above.

(5) Mrs. P., aged 22. Duration of labour: First stage 17 hours; second stage 1 hour.

The total loss in the third stage amounted to 8 oz.

The uterus did not contract down well following the birth of the placenta. It was atonic and filled up with blood and clots, 15 oz. of which were expressed from it. Further oxytocics were then given with success.

B.—Control Series

(1) Mrs. G., aged 33. Duration of labour: First stage 13½ hours; second stage 1½ hours.

Fairly brisk loss occurred while the placenta was still *in utero*. Credé's expression was performed, oxytocics administered, and good retraction obtained. There was no further hæmorrhage.

The total loss amounted to 25 oz., and the third stage lasted 15 minutes.

(2) Mrs. F., aged 23. Duration of labour 20 hours.

The placenta was still *in utero* one hour after the birth of the child. There was a slow trickle of blood. Credé's expression was accompanied by a gush of blood, much of which went into the bed. The loss in the receiver amounted to 24 oz. Oxytocics were given and there was no further bleeding.

Examinations of results will be made under the headings originally given. It is fully realized that deductions are of doubtful value in so small a series of cases, but it is felt that there are one or two observations that are worth recording.

(1) *Complications.*—One contraction ring, itself a considerable rarity, was encountered. Fortunately this did not in any great degree complicate treatment, but its potentialities are obvious. There are here two factors on which blame may be laid, namely uterine manipulations and pituitary extract.

(2) *The effect on hæmorrhage.*—(*a*) The incidence of post-partum hæmorrhage: This was more than doubled in the pituitary extract series, but again it must be emphasized that the series is small. An interesting point is provided by the fact that in two of the cases the placenta and membranes came away complete and the uterus contracted, the bleeding ceasing. Later the uterus relaxed, with further hæmorrhage, which in one case was profuse. It would appear from this that the oxytocic effect of pituitrin has a tendency to be transient—which has obvious disadvantages. (*b*) The average loss: If the cases of post-partum hæmorrhage are excluded, it is found that the average loss is 2 oz. less in the pituitrin series—a quantity of doubtful significance.

(3) *Duration of the third stage.*—An average reduction of about five minutes was noted here.

On these results one cannot feel that there is sufficient advantage or, for that matter, lack of disadvantage, to justify the routine use of pituitary extract in the third stage of labour.

There is, however, one type of case in which definite advantage is to be gained from this procedure, and I propose to conclude by quoting such a case, which I conducted recently.

Following a forceps delivery for prolonged second stage with threatened secondary uterine inertia, the uterus remained soft and there was steady loss. Attempts to rub up a contraction in order to perform Credé's expression were unsuccessful. Five units of pituitrin were accordingly given, following which a contraction was soon obtained and the placenta expressed complete with membranes without difficulty. By this means a manual removal was averted.

On the Effects of Pituitary Extract (Posterior Lobe) in the Third Stage of Labour

By R. C. Percival, F.R.C.S.

This paper deals with observations on the effects upon the third stage of labour of the intramuscular injection of 5 units of pituitrin (posterior lobe) directly, or very shortly, after the birth of the child, in 69 cases of labour in the Obstetric Department of the London Hospital. The observations were made during November and December 1938, and the preparation used was pituitrin (Parke, Davis), which contained both oxytocic and vasopressor substances. During the same period of time 74 control cases were observed and recorded under similar conditions. The two series of cases are compared. The Obstetric Department of the London Hospital, during the period of observation, consisted of two divisions. In Division I, the women were delivered by the medical students under the supervision of the House Surgeon to the Department. In Division II the women were delivered by the pupil midwives under the supervision of the Sister midwives. During the first month patients in Division I were given pituitrin as above described, whilst in Division II no pituitrin was given, 1 c.c. of ergometrine being injected after the delivery of the placenta. During the second month the procedure was reversed; that is, patients in Division II were given pituitrin, whilst those in Division I were not, but had an injection of ergometrine after the completion of the third stage. In Table II all cases are considered together, being divided into primiparæ and multiparæ, and into spontaneous and assisted labours.

Conduct of the third stage.—The third stage is conducted with the patient lying on her back and the attendant places the hand on the fundus uteri in order to detect changes in size, shape, and consistency of the uterus. So long as there is no undue external bleeding, or increase in volume of the uterus, whatever may be its consistency, massage or firm grasp of the uterus is not allowed. The hand is merely there to

TABLE I.—THIRD STAGE OF LABOUR.

Name — Age — Reg. No.
No. of previous labours
Abnormal previous 3rd stages
Type of labour
Duration of 1st stage
Duration of 2nd stage
Time baby born
Time pituitrin (5 units injected)
Time placenta delivered
Amount of hæmorrhage: Before / During / After — placenta delivered
Placenta
Weight — Complete
Diameter — Incomplete
Membranes
Complete
Incomplete
B.P. — Within 15 minutes of birth
Pulse — Within 15 minutes of birth
Remarks :
Uterine tone
Condition before injection, &c.

detect the signs of separation and descent of the placenta, or of accumulation of blood within the uterus (concealed bleeding). When the signs of separation and descent are manifest the placenta is pushed down the vagina by pressing the contracted uterus downwards in the direction of the pelvic axis ; when the placenta presents at the vaginal orifice it is removed by grasping and guiding it with ring forceps (sponge-forceps) or by gentle traction on the cord. Naturally enough, the patient sometimes succeeds in expelling the placenta by her own efforts, an attempt which she is always encouraged to make in suitable circumstances.

The amount of bleeding which occurred before, during, and after the delivery of the placenta was received into three separate bowls and measured.

TABLE II.

	Primiparæ		Multiparæ		Total	
	Spontaneous	Assisted	Spontaneous	Assisted	Spontaneous	Assisted
Test cases (pituitrin) ..	27	15	25	2	52	17
Control cases (no pituitrin)	27	7	39	1	66	8

Spontaneous test cases = 52.
Spontaneous control cases = 66.

Number of cases.—These are shown in Table II. The number of cases was 143, of which 69 were test cases and 74 were controls. The number of primiparæ and multiparæ, and of spontaneous and assisted labours, respectively, are shown in the table. The spontaneous deliveries amongst the test cases numbered 52, and amongst the controls 66. Spontaneous deliveries only have been used in the further analysis of the series. The 25 assisted deliveries are dealt with in a special section dealing with anæsthesia.

TABLE III.—DURATION OF 3RD STAGE IN MINUTES.

	Shortest time	Longest time	Average for P.	Average for M.	Average time
Test cases (pituitrin)	3	35	13	13	13
Control cases (no pituitrin) ..	1	50	16	12	14

The figures are given in minutes to the nearest whole number.

Duration of the third stage.—The cases are displayed in Table III. It is seen that there is very slight difference in the duration of the third stage whether pituitrin is given or not, the average duration being 13 minutes in the test group and 14 minutes in the control group. As a matter of possible interest, the average duration in multiparæ and primiparæ in both groups is compared.

TABLE IV.—AVERAGE AMOUNT OF BLOOD LOST.

	Before	During	After	Average for P.	Average for M.	Total Average loss
Test cases (pituitrin)	3	4	2	8	11	9
Control cases (no pituitrin	4	7	4	12	16	14

The figures are given in ounces to the nearest whole number.

Amount of blood lost.—The average amount of blood lost is given in Table IV, cases of post-partum hæmorrhage being included. It will be seen that the average loss is greater in the control cases than in the pituitrin cases, whether occurring before or after delivery of the placenta. Moreover, it will be noticed that in both series multiparæ bled more than primiparæ.

TABLE V.—21 CASES OF P.P.H. IN SPONTANEOUS DELIVERIES.

	No. of cases	Average duration of 2nd stage	Average duration of 3rd stage	Largest hæmorrhage	Smallest hæmorrhage	Average hæmorrhage
Test cases (pituitrin) ..	5	91′	21′	74 oz.	23 oz.	36 oz.
Control cases (no pituitrin)	16	63′	14′	64 oz.	20 oz.	34 oz.

The figures are given in minutes and ounces to the nearest whole number.

Cases of post-partum hæmorrhage.—These are shown in Table V. Post-partum hæmorrhage was said to have occurred when the amount of blood lost was 20 oz. or more. Using this definition, post-partum hæmorrhage occurred 21 times, or in 17·7% of the cases delivered spontaneously. It is difficult to account for this remarkably high incidence. Possibly, more accurate measurement than is made in the ordinary routine of midwifery practice may partly account for it. It is suggested that a probable explanation for many cases is that the pupil midwife or student failed to recognize that the placenta had left the uterus and therefore waited too long before delivering it. The fact that in the majority most of the bleeding occurred before or with the delivery of the placenta supports this suggestion. It is to be noted that 13 cases, or 62% of the total, occurred in the patients attended in Division II of the Department.[1]

The table shows that in this small series of cases there were more than three times as many cases of post-partum hæmorrhage when pituitrin was not given than when it was. The incidence of post-partum hæmorrhage in the test cases was 9·6%, and in the control cases was 24·2%. The average amount of blood lost in both sets of cases was roughly the same.

TABLE VI.—MEMBRANES.

	Complete	Incomplete
Test cases (pituitrin)	49	3
Control cases (no pituitrin) ..	58	8

Complications with delivery of placenta.—Credé's method of expression was used in four cases (in one pituitrin and in three control cases), excessive bleeding before the placenta had left the uterus being the indication in each case. No difficulty with the membranes was noted in the pituitrin cases ; as Table VI shows, defective chorion

[1] The detailed figures of cases of spontaneous delivery show that, in test cases, post-partum hæmorrhage was recorded in 13% of the cases in Division I and in 22% of the cases in Division II. In Division II, control cases, the rate was 31%, whilst in Division I it was 14%.

was recorded more often in the control cases. In no cases was it necessary to remove the placenta by the hand introduced into the uterus.

In one case a piece of placenta was retained in the uterus and was removed about twelve hours after labour for persistent bleeding. This patient died on the tenth day post-partum from pulmonary embolism. It was a case of spontaneous twin labour, and 5 units of pituitrin were injected intramuscularly after the second child had been born. During the next fifteen minutes 10 oz. of blood were lost, and after the placenta had been expelled from the vagina (it was not necessary to express it by Credé's method) another 12 oz. were lost. The large binovular placenta was rather ragged, but inspection led to the belief that it was complete. During the next twelve hours the patient had continuous slight loss of blood, so the uterus was explored by the hand and a piece of placenta found and removed, after which there was no further bleeding. Subsequently, a mild uterine infection, from a non-hæmolytic streptococcus, occurred, from which there was a quick recovery ; but the patient died from pulmonary embolism (confirmed by autopsy) on the tenth day.

TABLE VII.—EFFECT OF ANÆSTHESIA DURING 2ND STAGE.

	N_2O (spontaneous)			Ether (forceps breech or twins)			No anæsthesia (spontaneous)			
	No. of cases	Av. loss	%ge P.P.H.	No. of cases	Av. loss	%ge P.P.H.	No. of cases	Av. loss	%ge P.P.H.	%ge anæsth.
Test cases (pituitrin) ..	17	8 oz.	7	17	10 oz.	15	35	6 oz.	9	49
Control cases (no pituitrin)	22	12 oz.	13	8	15 oz.	60	44	15 oz.	30	41

Figures are given to the nearest whole number.

The effect of anæsthesia during labour.—The cases in which an anæsthetic was used are shown in Table VII. The cases so far discussed have been cases of spontaneous delivery, and it seems proper that only on such cases should the merits or demerits of pituitrin be decided.

Many of these cases received chloral hydrate but no anæsthetic except nitrous oxide, with air or oxygen, was given during the second stage of labour, and it was given in 33% of the test cases and in 33% of the control cases. In 25 cases of assisted delivery (forceps, breech, and one twin labour) nitrous oxide and ether were given. Reference to Table VII shows that the incidence of post-partum hæmorrhage is far higher in the control series than in the pituitrin series. The number of cases, however, is too small to be of value.

CONCLUSIONS

The number of cases is too small for the results to carry conviction. But so far as the investigation has gone, the intramuscular injection of 5 units of pituitrin (posterior lobe) directly after the birth of the child showed :—

(1) That the duration of the third stage was not appreciably affected.
(2) That the average loss of blood was less.
(3) That the incidence of post-partum hæmorrhage was less.
(4) That there was no tendency for chorion to be retained.
(5) That there was no tendency for a contraction ring to form.
(6) That there was no case of pituitrin shock.

The Effects of Injections of Pituitary Extract Immediately after Delivery

By S. G. CLAYTON, F.R.C.S., M.R.C.O.G.

THE following is a brief account of an experiment conducted at the suggestion of Mr. A. C. Palmer. The object of the experiment was to test the effect of giving 5 units of pituitrin immediately after the birth of the child, and to determine if the course of the third stage was altered. The experiment was not originally intended for publication and was in fact carried out by successive Housemen with varying

efficiency. While the test was going on Blomfield [1] published a series of 1,000 labours in which a similar test was made, and compared to that series the present series is insignificant.

The pituitrin was given to 83 primigravidæ and 34 multigravidæ. For comparison other cases delivered by the same staff were considered.

The duration of the third stage was noted. In all cases the placenta was expressed directly it was thought to have separated, but it is recognized that this observation is open to error, as the cases where pituitrin was given were more closely watched, so that separation might be sooner noticed. The table indicates the results :—

AVERAGE DURATION OF THIRD STAGE.

	Pituitrin given	Controls
Primigravidæ		
Normal delivery	14·8 min. (70 cases)	16·6 min. (186 cases)
Instrumental delivery	16·4 min. (13 cases)	18·1 min. (33 cases)
Total	15·0 min. (83 cases)	16·7 min. (219 cases)
Multigravidæ		
Normal delivery	10·1 min. (32 cases)	13·8 min. (143 cases)
Instrumental delivery	7·0 min. (2 cases)	10·1 min. (10 cases)
Total	9·9 min. (34 cases)	13·2 min. (153 cases)

It will be seen that the average duration of the third stage is reduced when pituitrin is given. The difference is not great, but is probably significant, as it applies to all the groups of cases. The same result was recorded by Blomfield. The number of cases in which the third stage exceeded the statutory half-hour were also noted, and it was found that 1 in 12 of the test cases had a third stage of over 30 minutes, and 1 in 13 of the control cases, an insignificant difference.

Then the amount of bleeding was considered. Although an attempt to measure the blood loss was made, it was found that such inaccuracies occurred that the average loss has not been considered, but only cases in which the loss definitely exceeded 20 oz. It is true that loss is often under rather than overstated, and a few cases may have escaped record on this account, but this applies to both groups of cases.

Among 117 test cases five had a loss of over 20 oz., an incidence of 4·2%, whereas among control cases the incidence was 3·8%, an insignificant difference.

Manual removal of the placenta was required five times among 372 control cases (three for hæmorrhage, two for retention of the placenta. Hour-glass spasm was not observed).

Among 117 test cases manual removal was performed three times, and in two cases retention was thought to be due to hour-glass spasm of the uterus, and here are the details of these cases.

The first was that of a primigravida who was normally delivered after 30 hours' labour. Five units of pituitrin were given immediately. After 50 minutes the placenta was still retained in spite of repeated attempts at expression and injection of saline up the umbilical vessels. As slow loss continued manual removal was attempted, and the house surgeon reported that a definite ring prevented the passage of the hand until amyl nitrite was given, when the ring was felt to relax and the placenta was easily removed.

The second was also a primigravida, who was delivered with forceps after 13

[1] BLOMFIELD, G. W. (1938), *Brit. M. J.* (ii), 1083.

hours' labour, and 5 units of pituitrin were given at once. Slow loss occurred and expression failed. After 20 minutes manual removal was attempted, and again a ring was felt, which only relaxed when amyl nitrite was given.

In the third case the placenta was removed after 2 hours' retention on account of bleeding, and there was no evidence of a ring.

The following conclusions may be put forward : (1) The average duration of labour was slightly shorter in cases where pituitrin was given. (2) The incidence of post-partum hæmorrhage of over 20 oz. was not reduced. (3) There is a danger of hour-glass spasm of the uterus, with the ensuing risk attached to manual removal of the placenta.

It may not be out of place to mention a case of uterine spasm noticed during lower segment Cæsarean section, when 10 units of pituitrin were injected directly into the uterine muscle. Spasm of the upper segment was so marked that it was not easy to extract the placenta, and a similar spasm may surely occur in occasional cases of normal labour where pituitrin is given, especially as the action of pituitrin on any particular uterus seems to be variable and unpredictable. It seems unjustifiable to expose the patient to this risk, however remote, just to obtain the doubtful advantage of shortening the third stage.

Mr. J. Wyatt said that it was at the instigation of Mr. Palmer, Mr. Lack, and himself, that this investigation had been carried out, as frequently they had heard it denounced (without sufficient evidence) as being dangerous. He felt that although the number of cases was not large, Messrs. Williams, Percival and Clayton had tabulated the results very well. With regard to those cases of " contraction ring " reported, it was rather difficult to lay the whole blame on the pituitrin as much manipulation of the uterus had been carried out before the complication was discovered. Lastly, he hoped that they would continue this work, as with a larger number of cases further points of interest might come to light.

Effective Methods of Using Oxytocic Drugs in Post-Partum Hæmorrhage

By Chassar Moir, M.D., F.R.C.S.Ed., F.C.O.G.

In 1935 I read before this Section a paper dealing with the merits and demerits of oxytocic drugs in the post-partum period. A cinematograph film has been prepared which illustrates and emphasizes certain of the matters which I then discussed, particularly the speed of action of the new ergot alkaloid, ergometrine, when administered by various routes (Dudley and Moir, 1935 ; Moir, 1935, 1936).

By means of a device strapped on the abdominal wall it is possible to study the behaviour of the uterus and to demonstrate the action of oxytocic drugs. A modification of this apparatus has enabled a cinema picture to be taken showing the time of onset of a uterine contraction. Ergometrine was found to act by the mouth in 5–10 minutes ; by intramuscular injection in about 3½ minutes ; by rectal injection in 3–10 minutes ; and by intravenous injection in 45 seconds.

The special object of this communication is to emphasize that in cases of post-partum hæmorrhage in which speed of action is essential, ergometrine should be injected intravenously in doses not exceeding 0·2 mgm. ; or, better, injected directly through the abdominal wall into the muscle of the uterus in a dose of 0·5 mgm. This latter means of administration has many advantages. It is simple, quick. safe, and efficient. Uterine response starts in about 15 seconds, and by 40 seconds the whole

organ becomes extremely contracted. A like effect is obtained when pituitary extract or the purified pitocin is similarly injected. I believe that this simple procedure is one of the most valuable therapeutic resources in midwifery, and by its use the need for hot intra-uterine douches or packing is almost eliminated. Except in the case of an abnormally fat patient, it is almost always possible to manœuvre the post-partum uterus so that it lies directly against the abdominal wall: the skin is then rubbed with tincture of iodine, and injection is made 1 in. or 2 in. below the umbilicus directly into the substance of the uterus. There is a theoretical danger that a rusty needle might snap during the injection, and for this reason only the modern stainless-steel type of needle should be used—this rule applies to intra-muscular injections of every variety.

Nothing new is claimed for this method of administering oxytocic drugs. Sir Beckwith Whitehouse has for many years advocated direct injection of pitocin into the uterus in cases of post-partum hæmorrhage, and Rawson in 1935 published an article emphasizing the usefulness of the method. After early doubts I am convinced that this is the method of choice in obstetrical emergencies.

The foregoing remarks refer to true post-partum hæmorrhage from a relaxed uterus. It may be asked whether a similar line of treatment is desirable in cases of third-stage hæmorrhage. This cannot be answered by a simple yes or no. It is unwise to administer any oxytocic drug as a routine measure before the placenta is expelled. If bleeding occurs from a relaxed uterus the orthodox lines of treatment are usually successful in promoting uterine contraction and arresting hæmorrhage. From time to time, however, every obstetrician is faced with a patient in whom the simpler forms of treatment have failed and in whom dangerous bleeding continues from a relaxed uterus. In such cases manual removal of the placenta is often contemplated. This operation has considerable dangers, and is followed in one-third of the cases by notifiable pyrexia. Before resorting to such a procedure it is, I believe, justifiable to inject 5 units of pituitary extract directly in the uterine wall. A hand should then be kept on the organ, and, after 40 seconds, when contraction is well established, a fresh attempt should be made to expel the placenta by Credé's manœuvre. This manipulation is frequently successful under the new conditions. It is important not to wait too long, as the excessive contraction induced by the drug may hinder rather than help the expulsion. If, however, the placenta is still found to be adherent it is wise to wait for half an hour before resorting to manual removal; by that time the pituitary effect will be nearly spent and the intra-uterine operation will be correspondingly easier.

Intra-uterine injection of pitocin or ergometrine in the third stage of labour is also, I believe, justified in certain cases of difficult delivery in which the patient has sustained a deep tear or cut of the cervix, vagina, or perineum. By this means the loss of blood, and the duration of time during which the patient has to remain semi-anæsthetized on the delivery couch, are both greatly diminished. Further, the actual work of repair is considerably facilitated, for the surgeon no longer has to contend with periodic gushes of blood which obscure the operation field. Again, I wish to emphasize that I do not advocate the administration of oxytocic drugs by this, or any other means, as a routine procedure in the third stage of labour. I have, however, used it unhesitatingly in particular cases in which the slight risk of incarceration of the placenta seemed to be the lesser of evils. On such occasions the injection has proved to be a very great boon.

REFERENCES

DUDLEY, H. W., and MOIR (1935), *Brit. M. J.* (i), 520.
MOIR, C. (1935), *Proc. Roy. Soc. Med.*, **28**, 116.
Id. (1936), *Brit. M. J.* (ii), 799.
RAWSON, W. F. (1935), *ibid.* (i), 1317.

The Elimination of the Breech Presentation from Private Practice

By G. F. Abercrombie, M.D.

In 37 patients out of a total of 181 the presentation at some stage of pregnancy was not cephalic. One of these, No. 91, was complicated by a central placenta prævia, was delivered by Cæsarean section, and need not here be further considered. A 20% incidence of breech presentation must, however, be an underestimate, for many patients did not come under observation until that phase of pregnancy was over. 15 patients were about to have their first baby, 13 their second, 5 their third, and 3 their fourth—an eloquent comment on the size of the modern family. The first-born children averaged 7 lb. 6½ oz. in weight, the others almost 7 lb. 14 oz. Twenty were male, 16 female.

It has been stated that a breech is of no importance before the 35th week, that external version is frequently followed by spontaneous reversion to the original position, and that such cases are best left alone, because there is probably some good obstetric reason for the abnormality. My experience does not confirm these ideas.

A breech presentation begins to be diagnosable about the 25th week, and in the weeks following may sometimes be the cause of a good deal of discomfort. Patients complain of unusual activity in the abdomen, of palpitation or faintness due to pressure on the "wind", of heartburn, of indigestion, of great breathlessness; of an abnormal sensation at the spot where the head is, of the child being very high up, of a cramp-like pain under the costal margin; also of frequency of micturition, and of being kicked in the appendix area or the bladder. These symptoms are relieved if the presentation becomes cephalic though spontaneous version may cause great distress. One patient wrote that she felt "both a physical and moral wreck after many hours of acute discomfort day and night. I don't know what's happened, but I feel quite different now, and the pressure is no longer on that very nasty spot".

Spontaneous version occurred in 22 patients, with one relapse, corrected later by external version. My conclusion is that in patients who have relatively large children, and whose muscles have not been stretched by frequent pregnancies, spontaneous version should normally be over by the beginning of the 33rd week. It follows that if we desire to imitate Nature, this, the 31st or 32nd week, is the best time to turn.

Explanation of the Diagram (opposite page).

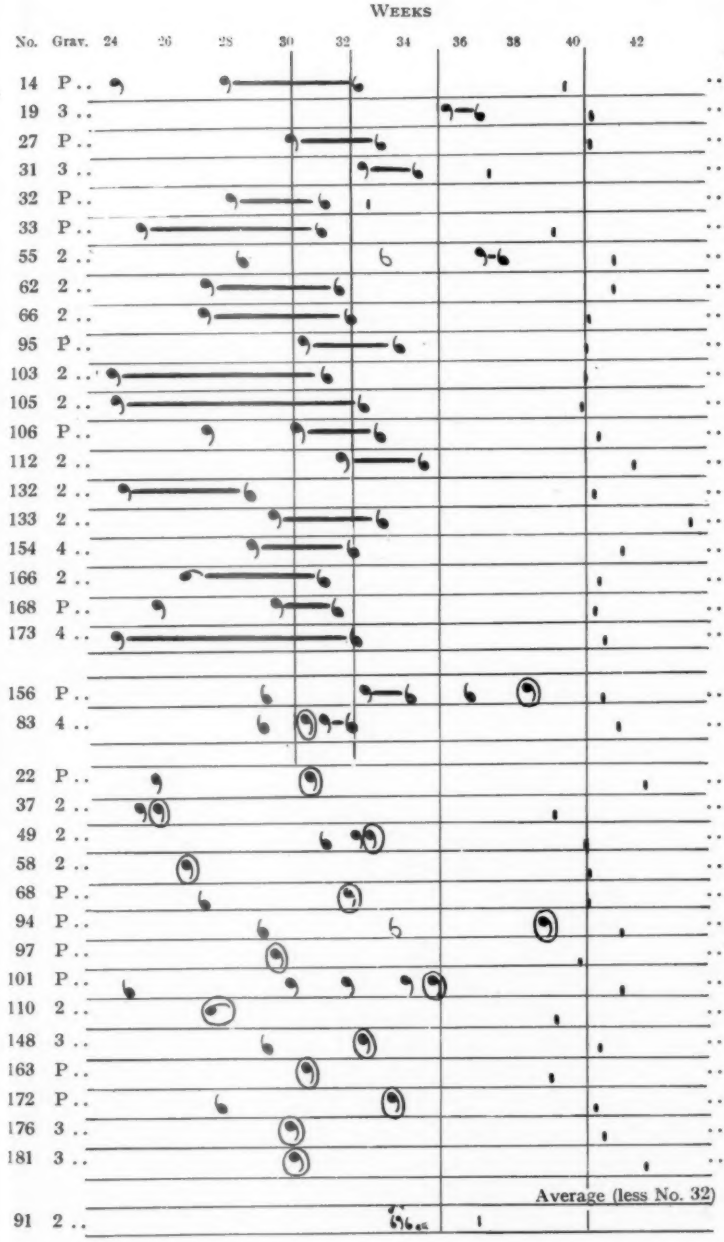
On the left are shown the serial number of the patient and the number of the pregnancy concerned. On the right is the child's weight, primigravida or multipara. In between is the stage of gestation in weeks, 24, 26, &c. Vertical lines emphasize the end of the 30th, 32nd, 35th, and 40th weeks. The serial numbers of the patients are repeated on the right.

The figure represents a breech, a transverse, a vertex presentation.

A horizontal line joining two figures indicates that spontaneous version occurred between those two dates.

The figure or enclosed in a circle—thus —indicates that external version was done at that time. Very many observations, here omitted for simplicity, were made in the later weeks of pregnancy to verify the final cephalic presentation. The end of pregnancy is indicated by a short vertical stroke.

In this diagram I have divided the cases, somewhat artificially, into the two groups of spontaneous and external version.



No.	Grav.	Child's weight: Prim.	Child's weight: Mult.	No.
14	P..	7·2		14
19	3..		8·12	19
27	P..	7·14		27
31	3..		7·2	31
32	P..	3·2 (S.B.)		32
33	P..	7·8		33
55	2..		7·13	55
62	2..		9·0	62
66	2..		8·0	66
95	P..	5·11		95
103	2..		8 8	103
105	2..		8·1	105
106	P..	7·8		106
112	2..		9·4	112
132	2..		6·11	132
133	2..		8·0	133
154	4..		6·15	154
166	2..		8·0	166
168	P..	7·8		168
173	4..		8·10	173
156	P..	8·5		156
83	4..		5·12	83
22	P..	8·0		22
37	2..		6·8	37
49	2..		7·0	49
58	2..		8·4	58
68	P..	7·0		68
94	P..	7·5		94
97	P..	10·0		97
101	P..	6·10		101
110	2..		8·0	110
148	3..		8·12	148
163	P..	6·0		163
172	P..	7·4		172
176	3..		7·1	176
181	3..		7·15	181
		Average (less No. 32) 7·6¼	7·14	
91	2..		5·8	91

External version was done in 16 patients, with one relapse only, which spontaneous version very soon corrected. It is noteworthy that in eight patients in this group a vertex presentation had been observed before the breech presentation was found. In other words, it has been my practice, on finding a breech presentation where I had previously found a vertex, to turn at once.

In two cases anæsthesia was used. One of these, No. 101, was very nearly a failure. At the 25th week, it was diagnosed a vertex ; at the 30th, a breech R.S.A. which I could not turn with a very half-hearted attempt ; at the 32nd, still a breech and version failed, though she thinks it became a vertex and reverted to a breech a day or two later ; at the 35th week external version was performed with great difficulty under anæsthesia. On a few other occasions I have essayed tentatively to see whether the breech would turn, but have not persisted in such efforts in relatively early pregnancy. No untoward signs have followed on any attempt, whether successful or not. At the end of the 35th week, only 4 breeches remain of the original 36. No. 19, a 3-para, turns almost at once. No. 156 is a surprise, for a breech is found in a primigravida in the 39th week long after spontaneous version, from breech to vertex, had occurred. It was immediately turned and kept under very close observation until term. The other two cases would almost certainly not have been allowed to present as breeches at this stage, if mistakes in diagnosis had not been made at the 34th week. No. 94 had to be turned under anæsthesia in the 39th week, and No. 55, after an attempt at external version had failed, fortunately turned spontaneously to vertex a few days later.

Thus when the time came, all these cases went into labour as vertices. The confinements were comparatively uneventful. No. 32, shortly after a spontaneous version, became the subject of a severe toxæmia, for which, as treatment proved of no avail, the pregnancy was terminated in the 33rd week. This is the only stillbirth, and you will agree that it cannot be indexed as due to the breech presentation. So the maternal and fœtal mortality are nil. Two multiparæ were induced for post-maturity by rupture of the membranes. Low forceps were used twice, and forceps were also used on a 10-lb. baby whose head suffered transverse arrest in mid-pelvis. All the other patients delivered themselves, one as a face, but there was no case of persistent occipito-posterior.

Prematurity, associated solely with a breech presentation, is conspicuously absent from this series.

I suggest, therefore, that there are five good reasons for insisting that a breech presentation be eliminated :—

(1) to relieve symptoms ;
(2) to lessen the risk of premature labour ;
(3) to fit the head into the brim ;
(4) to diminish fœtal mortality ;
(5) to reduce the number of Cæsarean sections performed on primigravidæ.

I must apologize for the small number of cases I have been able to bring before you. Nevertheless, they convince me that external version, performed early, is of the greatest value, and that the advantages of doing it early are as clear as the risks of attempting it late.

Section of Epidemiology and State Medicine

President—J. A. H. Brincker, M.B.

[*March* 24, 1939]

The Epidemiology of Jaundice

By E. R. Cullinan, M.D., F.R.C.P.

There are two forms of infective jaundice seen in this country, Weil's disease and common infective jaundice. Jaundice associated with other diseases, such as pneumonia, typhoid, and paratyphoid infections, does not come within the scope of this discussion.

Weil's Disease

I shall not say much about this disease. Excellent accounts of the epidemiology and references to the literature are given by Davidson and others (1934 and 1936) and by Alston and Brown (1937). Weil defined the entity in 1886 and Inada and Ido discovered the causal organism, the *Leptospira icterohæmorrhagiæ*, in 1915. Recently the disease has been recognized in this country, but is still relatively uncommon. Alston and Brown (1937) were able to refer to 142 cases collected from the literature and other sources from July 1933 to February 1937. Since then other accounts have appeared from Davidson (1938), concerning fish-workers in Aberdeen; Swan and McKeon (1938), coal-miners in N.E. England; Stuart (1938), Glasgow tripe-workers; Naftalin (1938), a case following violent immersion in a canal; Robertson (1938), four cases from the same stream in the south of England; Stuart (1939), Glasgow sewer-workers; and Rees (1939), six cases in miners from the South Wales coalfield.

Even up to the present time under 200 cases have been reported in Great Britain, although there is evidence of past infection in more.

Rats are almost always the direct or indirect source of infection in man. The excreted leptospira can remain alive in water, particularly in slime, but die quickly in an acid medium, in strong sunlight, or in salt water. They enter the body either through cuts and scratches on the sodden skin and also, some think, through the upper respiratory tract or even the conjunctivæ. These requirements narrow down the incidence of the disease to certain particular occupations of which sewer-workers, fish-workers, coal-miners, and bathers (particularly violent bathers), head the list.

The clinical picture and laboratory methods of diagnosis are now well known. The incubation period is usually seven to thirteen days. The mortality is in the region of 15%. Early diagnosis is important as it is then that antiserum is of greatest value. Not only are there the classical cases with sudden onset, headache, severe muscle pains, nausea and vomiting, prostration and fever, watery conjunctival suffusion and albuminuria followed in four to seven days by jaundice, but there are, as Davidson (1938) remarks, mild infections with fever and malaise but without jaundice. If, combined with these symptoms, there is a history of suitable occupation and circumstance, the disease should at once be suspected. Although uncommon, cases are more frequent than is supposed. Dr. Wolstencroft (1939), who has been

interested in the disease, tells me that he has seen three in three years in one small country town ; the first in a canal labourer (published 1935), the second in a gravel-pit worker, and the third in a worker in a rat-infested paper-mill on the banks of the canal.

In spite of endeavour, it seems unlikely that the particular occupational sites will be rid of rats and prevention of the disease will largely depend on prophylactic active immunization.

Common Infective Jaundice

Incidence.—Common infective jaundice (" catarrhal jaundice " ; " common infective hepatic jaundice ") is a frequent and widespread disorder in this country. The causative agent is unknown. It appears in epidemics, but cases which are apparently sporadic are also seen. As the clinical course is usually mild and the disorder is not generally notifiable, accounts of it are relatively few. Nevertheless, the number of cases recorded in different outbreaks in various localities is sufficient to form a fair sample of the whole. The following is a list of reports of outbreaks in this country which have appeared in the last twelve years. The list includes certain important unpublished epidemics, and I am greatly indebted to Dr. Brincker, Dr. Alison Glover, and Dr. J. L. Newman, for showing me the accounts of these and allowing me to quote from them.

Reports of Outbreaks of Epidemic Infective Jaundice in England : 1926–1939

Authors	Date of report	Place	No. of cases
Martland and Winner	1939	London	4
Newman	1939	Sussex (South)	130+
The School Epidemics Committee	1938	Different localities. 77 small outbreaks in various schools	158
Brincker	1938	London (L.C.C. schools, &c.)	193
Simpson (not yet published)	1938	Devon (Torquay)	5
Sergeant	1937	Durham (Gateshead)	49
Barber	1937	Derbyshire	?
Lisney	1937	Leicestershire	40
Pickles	1936	Yorkshire (Wensleydale)	19
Bates	1936	Gloucestershire (Stoke Park)	65
Ramage	1935	Lincolnshire (Holland)	26
Frazer	1935	Staffordshire (Newhall)	25
Beauchamp	1934	?	3
Bashford	1934	London (G.P.O.)	48
Montford	1934	Leicestershire (Castle Donington)	45
Booth and Martyn	1933	Lincolnshire (Holland)	13
Findlay, Dunlop and Brown	1931	Surrey	190
Glover and Wilson	1931	A country town	106+
Pickles	1930	Yorkshire (Wensleydale)	250
Butterworth and Brothwood	1930	Lancashire	25
Brown and Gardner	1927	Oxford (approx.)	*200
Morgan and Brown	1927	Midlands	200
Booth and Okell	1927	Surrey	106
			1900+

* Personal communication.

It will be seen that the outbreaks are widely scattered over the country and have taken place at different times. Yet, wherever the syndrome is seen, it has the same essential clinical and epidemiological features, suggesting strongly that it is one disease process and probably that it has one specific cause.

The disease is common and infective, and for these reasons I have called it common infective jaundice. This does not commit us to a pathology the exact nature of which is still sometimes disputed.

It is often said that the disease is one of rural areas. I doubt the truth of this. Plenty of cases are seen in London hospitals and in London schools (Brincker, 1939).

I think the idea of rural incidence has arisen simply because the disease is more easily seen and traced in small country villages and towns and therefore more often remarked and reported, especially as the incubation period is long and the infectivity often low.

Outbreaks usually start between the months of August and March, and may continue throughout the year, although the incidence is less in the summer months.

Epidemics involve communities of people who are in close contact with each other, as in schools and families, particularly in children of the school ages of 6 to 10. Children of pre-school age are not exempt. Adults, particularly young adults, are by no means immune. For example Bashford (1934) describes an outbreak of 48 cases in a section of the London General Post Office in which all the patients were adults, mostly young. In many of the general epidemics about a fifth of the patients were adults. Pickles (1930) suggests that the disease attacks all ages indiscriminately and that it is seen mainly among school children because the school provides the opportunity for infection. From the available data, however, it does seem that adults have more immunity than children, although the symptoms tend to be more severe. The sexes are equally affected.

Clinical features.—Common infective jaundice is milder than Weil's disease and clinically distinct. Its mildness in this country is characteristic. It should be remembered, however, that a severe case of the milder disease may possibly simulate a mild case of the more severe, and if there is the slightest doubt of the nature of an outbreak, Weil's disease should be excluded as quickly as possible.

The clinical features are remarkably constant, although the nature of the disease is usually not apparent until bile has appeared in the urine, or jaundice is seen.

Frequently, there is a prodromal stage of indefinite malaise from one to seven days before the onset of acute illness. In one epidemic (Glover, 1930) there was a prodromal period of lassitude lasting from three to four weeks. The onset starts acutely, usually with fever. The temperature may rise as high as 103° F., but falls again within the next day or two. This initial fever is seldom remarked, as the temperature is not often taken at the onset. The patient is usually described as having a " chill " or " huddled in front of the fire " (Newman, 1939), but there are no rigors. Headache is frequent for the first two or three days and occasional drowsiness. Loss of appetite is complete. Nausea is common. Vomiting, often severe and intractable, is characteristic though not invariable from the onset. Abdominal pain or discomfort is common, typically in the epigastrium and less often in the right upper quadrant of the abdomen. Jaundice appears in anything from 0 to 12 days from the acute onset, and is seen first in the conjunctivæ and then in the face and neck. In mild cases it lasts only a few days, but in the more severe it may persist for three weeks or more. The appearance of jaundice usually coincides with the beginning of convalescence and the end of the initial symptoms. On examination, in the early stages, there is often epigastric tenderness and, later, sometimes tenderness over the region of the gall-bladder or the enlarged liver. I have seen a case in an adult in which severe vomiting with epigastric tenderness had persisted for nine days ; then for the first time there was localized tenderness, worse on inspiration, just below the tip of the right ninth costal cartilage ; two days later there was jaundice. During the stage of jaundice the liver is frequently enlarged. My impression is that the longer the jaundice lasts the greater is the enlargement. In adults it is not unusual to find the liver extending down as much as three fingerbreadths below the right costal margin, although this is seldom found in children in whom the disease is shorter. In some epidemics the gall-bladder is said to have been palpable ; personally I have never been able to elicit this sign. The spleen is occasionally palpable. The urine contains bile pigments, and when this can be dated the urine is dark one or two days before the jaundice appears. This valuable sign is stressed by Dr. Newman (1939). I should like at this point to refer to a bedside test for latent jaundice worked out by Dr. Brodribb and myself (1936) which was first described by Klein (1931).

The equivalent of 0·1 mgm. of histamine in a one minim solution is injected intradermally into an area of skin devoid of sunburn or freckles. After ten minutes a wheal appears surrounded by a red zone. In good daylight, a piece of glass is pressed over the wheal and the colour of the centre compared with the colour of the skin outside the red zone. If there is a concentration of bile in the blood-stream corresponding to one unit of van den Bergh (0·5 mgm.% serum bilirubin) or more the centre of the wheal is distinctly yellow.

This is a useful bedside test for latent jaundice as one cannot recognize commencing jaundice with the naked eye until the bilirubin in the blood-stream has reached a concentration of nearly 4 units of van den Bergh (2 mgm.% serum bilirubin).

Bates (1936) draws attention to the presence of acetone in the urine when looked for early in the disease. A number of his cases had no vomiting, fever, or starvation, and he thinks it is due to a maladjustment between the fat and carbohydrate metabolism caused by hepatic damage. Albumin is occasionally seen in the urine, particularly in the more severe cases. The bowels may be constipated or loose with offensive motions. The stools are usually clay-coloured at some period of the illness, but frequently contain bile when jaundice is established. Blood: in contradistinction to Weil's disease there is no leucocytosis and often a leucopenia. There is a relative or absolute increase in lymphocytes or monocytes or both. Other symptoms: Probably because of the short duration of the jaundice itching is uncommon. Epistaxis is rare. Conjunctivitis is seldom seen. Urticaria is occasionally described. Peeling has been observed in a few cases. Sore throat is recorded in only a few epidemics. It was present in the early cases of the large school epidemic described by Glover and Wilson (1931) and in the three cases described by Beauchamp (1934). In the latter epidemic, however, although the throats were negative to K.L.B., there was a concurrent epidemic of diphtheria. I believe that sore throats are incidental and not really part of the clinical picture of the disease.

Convalescence.—Lasts from one to three weeks.

Severity.—The disease in this country is usually mild, especially among children. Morgan and Brown (1937) refer to two severe cases in an epidemic of 200. One of these died, and I will refer to the post-mortem findings later. My impression is that the disease is of longer duration and greater severity in adults than in children. Further, I am not convinced that the disease is always as mild as is supposed, but I will discuss this point later when speaking of subacute necrosis of the liver.

Recurrence.—Occasionally the disease recurs. Findlay, Dunlop and Brown (1931) refer to a case in which jaundice recurred two months after the primary attack, and Bates (1936) a boy of 8½ who had a second attack of jaundice thirty-four days after bile had disappeared from the urine; the second attack was more severe than the first. I know of a London surgeon who had the disease in childhood at least three times.

Complications.—Apart from the possibility of subacute necrosis of the liver, complications are very rare. Glover (1933) refers to one case of parotitis, and Martland and Winner (1939) to one of oöphoritis.

Method of spread.—Studying the epidemics as a whole, it can be said that the disease is not spread by water, milk, or food. It is quite clear that the spread is from person to person, and in a very large number of instances it is easy to trace the contact with others who had the disease or developed it shortly after. The contact is nearly always close; frequently relatives or children habitually sitting in the next seat to each other at school or sleeping in the same dormitory. The sole exception to this is in the epidemic described by Bashford (1934) in the London General Post Office, where the contact appeared only casual. The dormitory and family spread suggests a droplet infection.

Degree of infectivity.—The infectivity seems only high when contact is close, as in schools or similar institutions, or in families. Thus Glover (1930), reports that

in three schools 16%, 25%, and 33% of children were affected, but of the total 25 cases 19 were in family groups. A typical example of an epidemic was seen in Wensleydale (Pickles, 1930) where there were 250 cases among a population of 5,700 living in part of a valley less than twenty miles long. Each village had a good and separate water supply. There was constant communication between villages.

The incubation period.—The exact period of incubation is difficult to assess as the period of infectiousness is uncertain. An approximate time, however, can be estimated by studying the early cases of epidemics in homes where contact is close and members of the family often sleep together with little if any attempt at isolation. It is then seen that the cases occur either simultaneously or at spaced intervals of between twenty and forty days or, more probably, between twenty-one and thirty-five days. The following are typical examples :—

(1) A boy, aged 12, returned home from a preparatory school where there had been jaundice and at once developed the disease. His sister, aged 8, fell sick four weeks later ; the father thirty-one days after that ; then the mother after a further thirty days. (Findlay, Dunlop and Brown, 1931.)

(2) A family in a village in Wensleydale.

Aug. 16, 1929.	Jane.
Sept. 14, 1929.	James.
	Sarah.
Oct. 11, 1929.	William.
Oct. 12, 1929.	G. S. (Great friend of the family.)
Nov. 7, 1929.	Ann.
Nov. 6, 1929.	Jennie U. (A little girl, inseparable from the family.)
Dec. 4, 1929.	W. M. (Fiancé of Ann.)
Dec. 2, 1929.	D. U. (2-year-old sister of Jennie U.)
Dec. 29, 1929.	Jno U. (Father of the U. children.) (Pickles, 1930.)

(3) Five patients in three different villages whose only experience in common was that they attended a village fête a month before where they were in contact with a young girl suffering from jaundice. (Pickles, 1936.)

(4) An accidental infection of a laboratory worker as a result of working with serum from the Wensleydale epidemic of 1930. The possible incubation period was between thirty-one and forty-one days.

Dr. Glover tells me that he agrees that many epidemics have this long incubation period but believes that there is a form of the disease with a short incubation period of about four days. He arrived at this conclusion after a very careful study made by himself and Dr. Wilson (Glover and Wilson, 1931) of an extensive outbreak in a country town in which two boys' schools were involved. Many of the cases fell sick on the same day, and he thinks that it would have been very difficult for a disease with a long incubation period to have hit off one day so exactly. There was, however, no direct evidence that the incubation period was short, and they describe a case of a little girl who had been staying in the town who developed jaundice twenty days after leaving it, although there seemed no likelihood of infection during this latter period. As Findlay, Dunlop and Brown (1931) point out, an apparently short incubation period may be explained by A and B having been infected long before by X. Barber (1937) says that he has observed an epidemic in an institution with an incubation period of seven to eight days, but gives no details. Personally, I believe the evidence to be overwhelming that the incubation period is approximately between three and five weeks.

Period of infectiousness.—There is ample evidence that patients are infectious before they are jaundiced. The actual period of infectiousness must be short as shown by the extraordinary periodicity in families and small villages where there is little isolation and cases, often single, occur in series at an interval of about a month.

It is probably quite safe to return the children to school after two weeks. In adults, I do not hesitate to admit cases to the general wards of a hospital when jaundice is once established.

Carriers.—Sometimes unexplained gaps appear in an epidemic. For instance Newman (1939), who has studied an outbreak in the southern part of Sussex, found that it started in Arundel and Billinghurst at the end of 1937, died out shortly, recurred in different parts of the county in the summer of 1938, again died down, and then became established in October 1938 and still continues. It may be that there are carriers. Dr. Newman tells me that he has observed two separate cases arising where there could have been no possible contact with other patients. However, both had been in contact with people who themselves might well have been in contact with the disease.

Certainly, many cases are missed. Dr. Newman says that jaundice was found when looked for which would not have been identified as such under different circumstances. Moreover, in his epidemic, as in others, there are cases with initial symptoms followed by dark urine, without subsequent jaundice, and cases with initial symptoms with neither dark urine nor jaundice. The early appearance of bile in the urine is of importance. It may be fleeting, as shown by the following case described to me by Dr. A. W. Franklin (1939). It was at a time when he was seeing two or three cases of jaundice a week in the out-patient departments of two London hospitals. A child who had been vomiting and unwell for a few days, had a slightly tender liver but no jaundice. In the morning there were bile pigments in the urine; in the afternoon they had disappeared. The child made a quick recovery. These missed cases, the possibility of a carrier spread, the long period of incubation and sometimes the low infectivity, may explain why the disease is endemic in certain areas, and also why many cases appear to be sporadic. With regard to isolation, all children in schools with bilious attacks and vomiting during an epidemic should be isolated for a few days to see if they develop jaundice. No causative agent has been discovered. Leptospiral infection has been excluded. No convincing bacterial cause has been found. The disease cannot be transmitted to ordinary laboratory animals. These facts, together with the long incubation period, the clinical picture, and the absence of leucocytosis, suggest that the disease may be due to a virus infection.

Pathological Process of Common Infective Jaundice

The pathological process is probably, as was first suggested by Flindt in about 1890, a necrosis of the liver cells. Direct proof of this is difficult to obtain as opportunities for post-mortem examination of undoubted and uncomplicated cases of common infective jaundice are rare. Occasionally, however, during epidemics apparently typical cases adopt a severe clinical course ending in death. Two such cases in this country were reported by Morgan and Brown (1927) and Findlay and Dunlop (1932). Post-mortem findings showed liver-cell damage with no evidence of obstruction or infection of the bile-ducts. The criticism could be made that this was really a complication of the initial disease. A few descriptions appear in the literature of similar findings in cases in which a piece of liver had been removed for section at operation; for example Schrumpf (1932) and Nordmann (1925). Fortunately, there are two reports of patients who died as result of accidental death who at the same time appeared to be suffering from ordinary mild common infective jaundice. The first of these was reported by Gaskell (1933).

A girl, aged 5, was admitted to hospital for removal of tonsils and adenoids. The operation was performed under ether anæsthesia. The next day the child was jaundiced. On the following day, as a result of secondary hæmorrhage from the tonsillar bed, the patient died. In the village from which the child came there was at the time a true epidemic of infective jaundice and other

cases occurred both before and after the one described. At post-mortem examination there was general infiltration of Glisson's capsule with inflammatory cells. The liver parenchyma was swollen and degenerate. The bile epithelium was normal.

The details of the second case, as yet unpublished, have kindly been sent to me by Dr. H. Barber. The post-mortem material was studied by Dr. G. R. Osborn.

The case occurred in 1937 in Derbyshire where the disease was endemic. The patient, a man, aged 38, started his illness with nausea and vomiting. On the same day he fractured his skull. Four days later he was jaundiced, and on the eighth day he died as a result of the fracture. The liver showed early hepatitis without inflammation in the bile-ducts or duodenum.

Recently the view propounded by Virchow that common infective jaundice is really due to obstruction of the mouth of the common bile-duct has been revived by Hurst and Simpson (1934). They divide common infective jaundice into two diseases, one a true catarrhal jaundice due to temporary obstruction of the bile-duct, and the other a mild primary hepatic necrosis. They consider that there is clinical, biochemical, and histological evidence for this distinction. They say that in true catarrhal jaundice there is an initial gastritis with complete anorexia and nausea or vomiting, flatulence, epigastric discomfort, and pain, sometimes diarrhœa, furred tongue, and slight fever. The gall-bladder may be palpable when the patient is jaundiced. On the other hand, cases of mild primary hepatic necrosis seldom show pre-icteric symptoms of any kind, and the onset of jaundice is accompanied by symptoms of toxæmia such as headache, weakness, loss of appetite, and occasional vomiting and diarrhœa. There is slight fever, no epigastric tenderness, the liver is tender and slightly enlarged, the spleen is always palpable. Jaundice is less marked than in " catarrhal jaundice " and bile is always present in the stools. The condition lasts longer than true catarrhal jaundice.

In my experience, however, in a single epidemic both clinical pictures may be found at the same time. For instance, jaundice may appear from 0 to 12 days after the onset. Further, I have seen cases of subacute necrosis of the liver in which there was no suggestion at necropsy of obstruction or inflammation of the bile-ducts which had just such a history of initial gastritis as is described in the true "catarrhal jaundice". In these, the stools were often clay-coloured in the early stages. The spleen was only palpable in less than a third of the cases. Hurst and Simpson say that in true catarrhal jaundice the lævulose tolerance test was normal in nine out of ten patients, whereas in a case of primary hepatic necrosis there was evidence of hepatic insufficiency. But it is generally agreed that an impairment of lævulose tolerance depends on the degree of liver damage, and that this damage must be extensive before changes in tolerance are found. In one of the cases of subacute necrosis to which I have referred, the lævulose tolerance test was normal in the first attack of jaundice and impaired in the second.

In my opinion the van den Bergh test is of no value in distinguishing between jaundice caused by obstruction and jaundice caused by parenchymal damage of the liver cells.

Finally it is said that in true " catarrhal jaundice " the parenchymal necrosis is mainly in the central zone of the lobule, and that obstruction of the bile-ducts with cholangiectasis is a condition which constantly brings about such a central necrosis by pressure alone. With this I agree, but an initial central necrosis is also the outstanding characteristic of primary acute necrosis of the liver where there is no question of obstruction. Fig. 1 is a section taken from the liver of a patient who died from acute liver necrosis in pregnancy. The centres of the lobules are acutely fatty ; the cells at the periphery are relatively normal. Fig. 2 is a section from another case of acute necrosis in pregnancy and shows extensive degeneration of the lobules, especially in the centre.

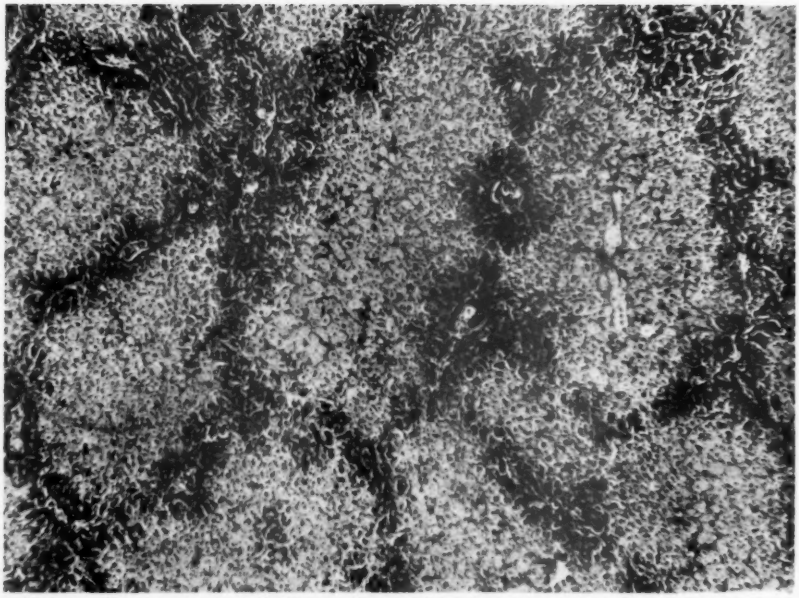


FIG. 1.—Acute necrosis of the liver. Centre of the lobules acutely fatty. Cells at the periphery relatively normal. (× 50.)

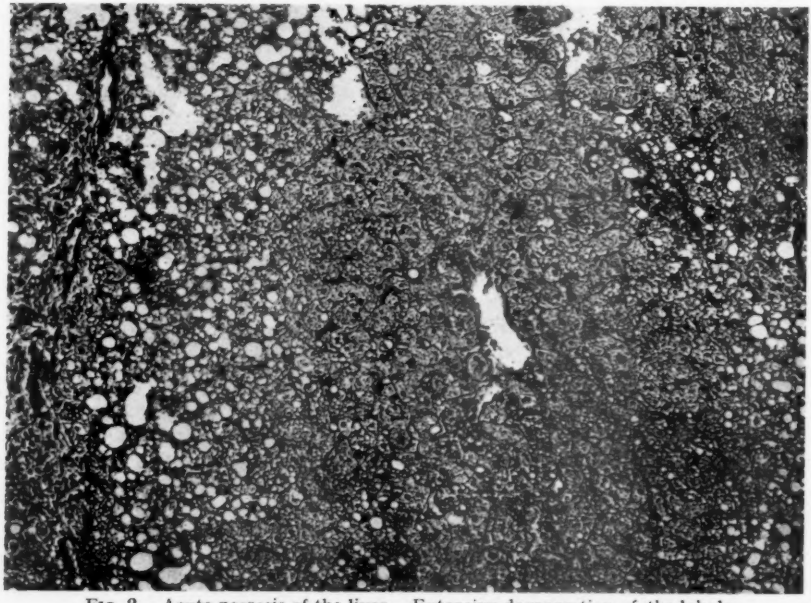


FIG. 2.—Acute necrosis of the liver. Extensive degeneration of the lobule, especially in the centre. (× 100.)

Figs. 1 and 2 from St. Bartholomew's Hospital Reports, 1936, **49**, by permission of the Editors. Blocks kindly lent by Messrs. John Murray, Ltd.

I do not believe that there is convincing evidence that common infective jaundice, as seen in Britain, has two separate pathologies. The much-quoted Gallipoli epidemic is hardly a fair criterion. The exact nature of this epidemic, occurring in a population saturated with paratyphoid B, was never settled. Such knowledge as we have of the disease in this country points to the jaundice resulting from damage of the parenchymal cells of the liver and not from a blocking of the common bile-duct or an ascending cholangitis. If the two conditions do exist, I should regard them as clinically indistinguishable from each other.

The Relation of Common Infective Jaundice to Acute and Subacute Necrosis of the Liver

Occasionally common infective jaundice ends with severe liver necrosis and death. I have already referred to two such cases in this country (Morgan and Brown, 1927; Findlay and Dunlop, 1932). In Sweden, Bergstrand (1930) reported a large number of instances. In Stockholm, between the years 1914 and 1925, there were on the average two cases a year of acute yellow atrophy. In 1925 and 1926 epidemic jaundice was rife throughout the country. In 1926 the incidence in Stockholm of acute yellow atrophy increased and in 1927 there were 42 cases. It might be said that epidemic jaundice in Sweden is not comparable with the disease seen in England. I am going to suggest that subacute necrosis of the liver unassociated with any known drug or toxin is in fact quite frequently seen in this country. In 1936 (Cullinan 1936) I published an account of 20 cases with post-mortem findings. These had been found mostly in one large London teaching hospital. Since that time I have seen many more proven cases and a larger number in which the diagnosis was made on clinical evidence alone. The clinical picture is remarkably similar, apart from its greater severity, to that of common infective jaundice.

The disease is characterized by attacks of jaundice. The attacks are often accompanied or preceded by vague symptoms of ill-health and gastric disturbance. These initial symptoms seldom persist after the jaundice is fully established.

During the height of the attack the patient feels moderately well. There is no fever, no mental disturbance, no loss of weight, and rarely any pain. Occasionally there is nose-bleeding.

There is usually enlargement of the liver and sometimes of the spleen. The colour of the stools varies from time to time but is seldom clay-coloured when the jaundice is established. Bile is found in the urine. There is moderate anæmia, but no leucocytosis. Van den Bergh's test is positive, both direct and indirect. Tolerance to lævulose is lowered. On X-ray examination the gall-bladder fails to concentrate dye.

The intensity of the jaundice varies in different cases and tends to fluctuate during the course of the disease. The jaundice may last for weeks or months. If the attack is not fatal, recovery may be complete, but after a period of good health varying in time from a few weeks to many years, the jaundice may recur.

In cases of long standing there may be hæmorrhages and signs of ascites.

When the attack is fatal, death usually results from liver failure, the symptoms and signs of which appear only in the last few days of life.

Histologically, there is subacute necrosis of the liver parenchyma affecting particularly the centre of the lobules. The bile epithelium is seldom destroyed, and the extralobular bile capillaries stand out prominently. The bile-ducts in the liver are not dilated and do not contain bile. There is no evidence of obstruction or inflammation of the larger bile-ducts.

In the absence of further epidemiological data it is difficult to say whether some or all of these cases are directly related to common infective jaundice. Subacute necrosis is caused by many agents, and although the cases here reported appear identical in their clinical and morbid anatomical appearances with those described by Bergstrand, this does not prove the relationship. The similarity, however, between these cases of subacute necrosis of the liver and cases of common infective jaundice is so close as to suggest that one of the causes of subacute necrosis is identical with the cause of common infective jaundice.

Relation of Common Infective Jaundice to Jaundice Observed in A Diabetic Clinic

Graham (1938) described an outbreak of jaundice in a diabetic clinic of a London hospital. The first case was noticed in May 1935, and during the next two and a half years there was a series of 28 cases. The epidemic has now ceased, and there have been no further cases in the last year. The patients in this clinic sat closely together on a bench in the out-patient hall. Graham points out that similar experiences have not been had in other diabetic clinics in London. The symptoms were identical with those of common infective jaundice except that the jaundice persisted for a long time and the diabetes was made worse. The shortest duration of jaundice was thirty-one days and the longest ninety.

It would appear that these were cases of common infective jaundice. It is possible that the greater duration of the disease in these patients may have been associated with a lowered resistance of the liver.

Relation of Common Infective Jaundice to Jaundice following Injections of Arsphenamine

There is no doubt that certain drugs given in large doses are sometimes followed by jaundice and necrosis of the liver. One example is salvarsan and its derivative used in the treatment of syphilis. Many years before the introduction of salvarsan it was known that syphilis was sometimes accompanied by jaundice and acute necrosis of the liver. Weber (1909) gives a bibliography of 53 cases up to the year 1908. Since the introduction of salvarsan the incidence of jaundice has risen. Thus Wile and Sams (1934), surveying the treatment of over 10,000 cases of syphilis, found that jaundice occurred seven and a half times more frequently in those patients who had been given salvarsan than in those who had not. The interesting feature is that a large number of cases of so-called post-salvarsan jaundice occur in epidemics irrespective of the preparation of the drug or the way in which it is given. Stokes, Reudemann and Lemon (1920) say that of 5,200 cases of syphilis treated in the Mayo Clinic from August 1916 to July 1920 there were six cases of jaundice in the first two years and 64 in the second. The methods of treatment over the four years were the same. Similar experiences are reported from other parts of the world. Bodin (1921), in France, found that in 254 cases of syphilis treated with arsenobenzols between the years 1912 and 1914 there were only two cases of jaundice. In 1921, 472 patients were treated and there were 34 cases of jaundice. Ruge (1925), reviewing the incidence of jaundice in the German Navy, states that the number of cases of epidemic infective jaundice rose considerably in the years from 1919 to 1923. Parallel with this rise there was a similar increase in the number of cases of so-called salvarsan jaundice without any alteration in the mode of treatment. Thus, of all syphilitic patients under treatment: in 1919, 3·7% developed jaundice; in 1920, 7·14% in 1921, 12·70%; in 1922, 10·60%; and in 1923, 20·37%. He suggests that so-called salvarsan jaundice is really ordinary infective jaundice in which syphilis and salvarsan occur as supporting agents in the origin of the disease. There were no clinical differences between the ordinary infective jaundice and the post-salvarsan cases except that the latter tended to be rather more severe and of longer duration. Richards (1933), gives an interesting account of an epidemic in the venereal clinic of a hospital in the Midlands. Commencing in April 1931 there was a series of over 120 cases of jaundice among patients receiving antisyphilitic treatment with salvarsan derivatives. The number of cases was in a ratio of one in every three. The great majority occurred among men. The disease in some was very mild, but in others sufficiently severe to require in-patient treatment. Sometimes the jaundice came soon after an injection, but in a few it was not until several months had elapsed. Alterations were made in the preparation of the drug without result. Eventually

jaundice appeared in a man who had received bismuth alone. The patients had to wait in a crowded passage and in 1932, owing to a great increase in the number requiring treatment, the crowding became acute. As soon as efforts were made to avoid excessive crowding there was a definite drop in the number of cases of jaundice. In August 1933 it was decided that all patients must wait in a large and well-ventilated out-patient hall and be admitted to the clinic in small numbers. The immediate result of this was a rapid fall in the incidence of jaundice.

Jaundice following arsphenamine is frequently delayed. Wile and Sams (1934) found that two-thirds of their cases occurred at an average interval of eighty days after the last injection had been given. However, as shown by Richards, the time after the last injection that the jaundice appears is by no means constant. Todd (1921), recording experiences in the Rhine army, says that he saw no cases of jaundice in patients having arsphenamine during the period from March to September 1920, but in October 1920 there were 24 cases with one death. The time of onset after the last injection varied from 1 to 119 days.

It is not suggested that jaundice cannot be produced by arsphenamine alone if a large enough dose is given. It seems clear, however, that a great number of cases of ordinary post-arsphenamine jaundice occur in definite epidemics and at the same time as epidemics of common infective jaundice. The interval between the onset of jaundice and the last injection of the drug is widely variable. Considering these facts, together with the similarity between the clinical and epidemiological features of the diseases, it would appear that post-arsphenamine jaundice is often identical with common infective jaundice. The greater severity of the clinical symptoms suggests that syphilis and salvarsan are supporting agents, which render the liver more susceptible in the origin of the disease.

Relation between Common Infective Jaundice and Jaundice following Inoculation against Certain Diseases

(*a*) *Yellow fever post-inoculation jaundice.*—Findlay and MacCallum (1938) recorded that among 3,100 persons immunized against yellow fever with virus and homologous immune serum over a period of five years, 89 cases of jaundice had been traced. The interval between the inoculation and the onset of jaundice varied from thirty-six days to just under seven months: the average interval was between two and three months. The cases almost always tended to occur in groups in regional areas. The disease was not yellow fever, and the symptoms closely resembled those produced by common infective jaundice, cases of which have frequently been noted as occurring in the same areas.

In two instances the syndrome started four weeks after exposure to infection with common infective jaundice. In a recent paper Findlay, MacCallum and Murgatroyd (1939) say that since another strain of the attenuated tissue culture virus has been used no jaundice has occurred among the 2,500 people inoculated. They give evidence to show that an extraneous hepatotoxic agent having many of the characters of a filtrable virus had been introduced into the former yellow-fever vaccine by the vehicle of apparently normal human serum. They postulate that this agent, probably a virus, is identical with the causative agent of common infective jaundice. They make the important recommendation that pools of apparently normal human serum should not be used for human inoculation, unless the medical history of all the donors can be followed for at least one month. One would suggest that this period should be extended to six weeks and that the donors should have no history of jaundice in the past.

(*b*) *Measles post-inoculation jaundice.*—A similar outbreak has been seen after inoculation against measles. MacNalty (1938) reports that among 82 to 109 persons inoculated with human serum from one batch there were 37 cases of jaundice, seven of which were fatal. More recently a further series occurred. A widespread inquiry

was made in this country, in Europe and in America, but no similar sequence of events could be traced. The report refers to these cases as acute infective jaundice not to be confused with epidemic catarrhal jaundice, but as I have said, I do not believe that the distinction can be made. Jaundice appeared from 16 to 100 days after the inoculation. The symptoms and physical signs of the majority differed little from those of the so-called " epidemic catarrhal jaundice " which had been prevalent in the district mainly affected. The same conclusions can be drawn as in the yellow-fever post-inoculation cases, that a hepatotoxic agent was present in the apparently normal human serum, and that the same precautions in administration are necessary.

There seems little doubt that both yellow-fever and measles post-inoculation jaundice are identical with common infective jaundice. But the jaundice develops at widely varying times after the inoculation, usually long after the normal incubation period of common infective jaundice and also the cases occur in areas where common infective jaundice is known to exist. It seems possible that a hepatotoxic agent, perhaps a virus or substance in the serum of donors who have or have had common infective jaundice, was introduced by the inoculation, and that this agent did not itself cause but predisposed to a subsequent infection of the disease, often in a more severe form.

REFERENCES

ALSTON, J. M., and BROWN, H. C. (1937), *Proc. Roy. Soc. Med.*, **30**, 741.
BARBER, H. (1937), *Brit. M. J.* (i), 67.
Id., Personal Communication, 1939.
BASHFORD, H. H. (1934), *Lancet* (ii), 1008.
BATES, R. (1936), *Brit. M. J.* (i), 521.
BEAUCHAMP, A. (1934), *ibid.* (i), 850.
BERGSTRAND, H., " Über die Akute und Chronische Gelbe Leberatrophie ". Georg Thieme, Verlag, Leipzig, 1930.
BODIN, E. (1921), *Bull. Soc. Franc. de dermat. et syph.*, **28**, 242.
BOOTH, W. G., and MARTYN. Rep. of County Med. Off. Lincs. (Holland), 1933.
BOOTH, W. C., and OKELL, C. C. (1927–28), *Pub. Health*, **41**, 237.
BRINCKER, J. A. H., Personal Communication, 1939.
BRODRIBB, H. S., and CULLINAN, E. R. (1936), *Lancet* (i), 1237.
BROWN, H. E., and GARDNER, A.. D., *Ann. Rep. of Med. Res. Council*, 1927–28, p. 52.
BUTTERWORTH, J. J., and BROTHWOOD, W. C. V., Ann. Rep. of Med. Off. Health. Lancs. 1930.
CULLINAN, E. R. (1936), *St. Barth. Hosp. Rep.*, **49**, 55.
DAVIDSON, L. S. P. (1938), *Glasgow M. J.* (ii), 113.
DAVIDSON, L. S. P., CAMPBELL, R. M., RAE, H. J., and SMITH, J. (1934), *Brit. M. J.* (ii), 1137.
DAVIDSON, L. S. P., and SMITH, J. (1936), *Quart. J. Med.*, **5**, 263.
FINDLAY, G. M., and DUNLOP, J. L. (1932), *Brit. M. J.* (i), 652.
FINDLAY, G. M., DUNLOP, J. L., and BROWN, H. C. (1931), *Tr. Roy. Soc. Trop. Med. & Hyg.*, **25**, 1, 7.
FINDLAY, G. M., and MACCALLUM, F. O. (1938), *Proc. Roy. Soc. Med.*, **31**, 799.
FINDLAY, G. M., MACCALLUM, F. O., and MURGATROYD, F. (1939), *Tr. Roy. Soc. Trop. Med. & Hyg.*, **32**, 5, 575.
FLINDT (1890), *Bibliot. f. Læger*, p. 420. Quoted by WALLGREN, A. *Acta Med. Scandinav.*, 1930 (Suppl. No. 26), 118.)
FRANKLIN, A. W. Personal Communication, 1939.
FRAZER, E. M. R. (1935.) *Brit. M. J.* (i), 701.
GASKELL, J. F. (1933), *J. Path. & Bact.*, **36**, 257.
GLOVER, J. A. Personal Communication, 1939.
GLOVER, J. A., and WILSON, J. (1931), *Lancet* (i), 722.
GRAHAM, G. (1938), *ibid.* (ii), 1.
HURST, A. F., and SIMPSON, K. (1934), *Guy's Hosp. Rep.*, **84**, 173.
INADA, R., and IDO, Y. (1915), *Tokyo Ijishinshi*, p. 1908.
KLEIN, O. (1931), *Klin. Wchnschr.*, **10**, 2032.
LISNEY, A. A. (1937), *Brit. M. J.* (i), 703.
MACNALTY, A., Ann. Rep. of the Ch. Med. Off. of the Min. of Health for the Year, 1937, H.M. Stationery Office, London, 1938.
MARTLAND, E. M., and WINNER, A. L. (1939), *Lancet* (i), 161.

MONTFORD, T. M. (1934), *Brit. M. J.* (i), 330.
MORGAN, M. T., and BROWN, H. C., Ministry of Health Rep. on Public Health and Med. Subjects, H.M. Stationery Office, London, 1927. No. 42.
NAFTALIN, R. (1938), *Brit. M. J.* (i), 621.
NEWMAN, J. L., Personal Communication, 1939.
NORDMANN, E. (1925), *Med. Klin.*, **21**, 1746.
OSBORN, G. R., Personal Communication, 1939.
PICKLES, W. N. (1930), *Brit. M. J.* (i), 944.
Id. (1936), *Brit. J. Child. Dis.*, **33**, 192.
RAMAGE, G. (1935), *Pub. Health*, **48**, 391.
REES, W. E. (1939), *Brit. M. J.* (i), 603.
RICHARDS, R. M. (1933), *Proc. Derby Med. Soc.*, p. 32.
ROBERSTON, K. M. (1938), *Brit. M. J.* (ii), 1300.
RUGE, H. (1925), *Ztschr. f. klin. Med.*, **101**, 684.
Id. (1926), *ibid.*, **103**, 272.
SCHOOL EPIDEMICS COMMITTEE, Med. Res. Council Spec. Rep. Series, 1938, No. 227, 200.
SCHRUMPF, A. (1932), *Ann. d'anat. path.*, **9**, 17.
SERGEANT, B. (1937), *Brit. M. J.* (ii), 703.
SIMPSON, J. V. A., Personal Communication, 1939.
STOKES, J. H., RUEDEMANN, R., and LEMON, W. S. (1920), *Arch. Int. Med.*, **26**, 521.
STUART, R. D. (1938), *Lancet* (i), 604.
Id. (1939), *Brit. M. J.* (i), 324.
SWAN, W. G. A., and MCKEON, J. A. (1938), *Lancet* (i), 201.
TODD, A. T. (1921), *ibid.* (i), 632.
WEBER, F. P. (1909), *Proc. Roy. Soc. Med.*, **2**, 113.
WEIL, A. (1886), *Deutsches Arch. f. klin. Med.*, **29**, 209.
WILE, U. J., and SAMS, W. M. (1934), *Am. J. M. Sc.*, **187**, 297.
WOLSTENCROFT, J., Personal Communication, 1939.
Id. (1935), *Lancet* (i), 86.

Discussion.—Dr. J. D. ROLLESTON said that though he could not claim much practical experience of epidemic jaundice, his interest in the subject had been shown by his summaries of the literature in the *Medical Annual* for the last twenty years. Recent articles had drawn attention to the increasing frequency of leptospiral jaundice in Great Britain, especially among sewer-men, miners, and fish-workers, and had suggested the employment of prophylactic measures such as inoculation and the destruction of rats (Rees). Abortive forms simulating aseptic meningitis in which no jaundice was present were frequent, and could only be diagnosed by an agglutination test. Dr. Rolleston inquired if any members had had experience of leptospiral jaundice following bathing, of which numerous examples had occurred in Holland, where the closure of the swimming bath at Dordrecht, one of the towns most affected, was followed by a remarkable fall in the incidence of the cases (Jitta).

References.—REES, W. E. (1939), *Brit. M. J.* (i), 603; JITTA, N. M. J. (1934), *Bull. Office internat. d'hyg. pub.*, **26**, 688.

Dr. J. L. NEWMAN said that an endemic focus of jaundice was found to have existed in Arundel since July 1937, but it did not spread outside till April 1938. Since then seven widely separated foci had appeared in the North; but the main spread has been along the coastal plain, and so to ten centres, with a particularly heavy incidence in the Bognor district.

There had been two seasonal peaks, one in November (60 cases) and one in January (87 cases). As in the Medical Research Council Report there had been little tendency to spread in schools, and of the 39 involved, 20 had produced three or less cases, and only four 25 or more. The important role so often attributed to schools in favouring spread might be more apparent than real and due to the age of maximum incidence being 6–10 years.

Two particular outbreaks had been mentioned. At Slindon, the village as a whole escaped, and there was no spread in the school. All the cases were concentrated in a single row of houses just outside the main village, and the proportion of adults attacked was relatively high: seven school children, one adolescent, four adults. At Aldingbourne there had been 65 cases involved over a wide area. Spread seemed to have been entirely through the school (55 cases out of 180 children): another small school close by was not involved till the outbreak was over, and adjacent and contiguous villages escaped entirely. The classroom might have had some influence since the infants' room was not involved till seven weeks after the onset. Direct contact was likely in most cases, but two suggested the possibility of carriers.

(1) An isolated cottage used as a home for low-grade mentally defective children (mostly cot cases) had one case. The two attendants had been well and the parents came from an uninfected district. Bottled milk was delivered by a boy who had the disease thirty-one days before, but none of his other customers was infected.

(2) A remote cottage said to have been entirely cut off by the very bad weather at Christmas had 2 cases. Two children attended the village school and remained well. Their brother, aged 4, had been confined to the house with a severe attack of impetigo for six weeks before, on January 14, he sickened with jaundice. His father sickened one week later.

Atypical cases might be of epidemiological importance. In three schools the teachers volunteered the information that there had been an unusually high rate of absence for " biliousness " before the jaundice cases appeared. Among the atypical cases quoted were :—

(1) Eileen W. October 5 sickened for a typical attack.
Norman W. October 25 sickened for a typical attack.
Mrs. W. November 13 vomited all day, poorly, ached all over. 14th better, but sharp abdominal pain. Later the urine was dark, stools clay coloured, and the family noticed just perceptible jaundice ; the patient would not have noticed this herself.

(2) George H., aged 7. December 20 sickened for a typical attack.
Susan H., aged 4. January 17 sickened for a typical attack.
Mrs. H. February 17–20 vomiting, anorexia, and malaise. No pain or evidence of bile.

Dr. Newman summarized his observations as follows :—

(1) " Biliousness " may precede an outbreak of jaundice.

(2) School outbreaks tend to fizzle out without serious spread : the liability to spread in schools has been overrated.

(3) House-to-house infections may occur but are relatively unimportant.

(4) Carriers may provide the means of propagation.

(5) Atypical cases, recognized as jaundice only in the presence of other cases, or even unrecognized, may be of epidemiological importance.

(6) Clinical features were so variable as to make futile any attempt to differentiate by their means different types of upper abdominal disease.

Major H. C. Brown said that he was glad to hear that Dr. Cullinan did not advocate the subdivision of epidemic catarrhal jaundice into two distinct diseases.

He would like to ask Dr. Cullinan what his views were on the degree of immunity conferred by an attack of this disease. Working with Dr. Morgan in the Northamptonshire epidemic, they were of opinion that villages showing a high rate of infection one year showed few cases in the following year.

Dr. Cullinan had referred to jaundice following the administration of measles immune serum and also to the necessity for accurate diagnosis as early in the disease as possible. He had had the opportunity of examining one of the earliest cases of jaundice after measles serum ; this case had been diagnosed as being Weil's disease, but from the total absence of antibodies to the *Leptospira icterohæmorrhagiæ* and from the results of animal inoculation, he was able to exclude Weil's disease. Furthermore, in this case, the absence of leucocytosis and the high mononuclear differential blood-count pointed very strongly to the condition being one of epidemic catarrhal jaundice.

He would finally like to ask Dr. Cullinan whether he knew of any clinical symptoms or physical signs which would enable anyone to differentiate between a really florid case of epidemic jaundice and one of Weil's disease, as apart perhaps from the intense muscular pain in the latter he thought that the differential diagnosis on purely clinical grounds was extremely difficult if not impossible.

Dr. J. A. Glover agreed the evidence that one type of epidemic catarrhal jaundice had a long incubation period seemed conclusive. He suggested there was a second type with a short incubation period, in which tonsillitis was often a prominent symptom, and in which cases of tonsillitis without jaundice were seen alongside the cases of jaundice. Such seemed to be the epidemics described by Chomet in Vienna in 1933, by Dr. J. Wilson and himself in Dorset in 1930, and that at Burton-on-Trent in 1935 by Dr. E. M. R. Frazer, in which in every case of the 25 described there was a common symptom of sore throat. Dr. Frazer, however, had not stated the incubation period. H. Barber had been fortunate enough to observe two epidemics

of catarrhal jaundice in one institution, the first with a short (seven to eight days') incubation, the second with one of twenty-five days.

He contrasted with these the Woolplumpton epidemic of 1930 reported by Dr. Brothwood, in which no sore throat was reported, or the long incubation type epidemic at Newbold Verdon in 1936 reported by Dr. A. A. Lisney, where only one out of 40 cases had sore throat. Dr. Glover

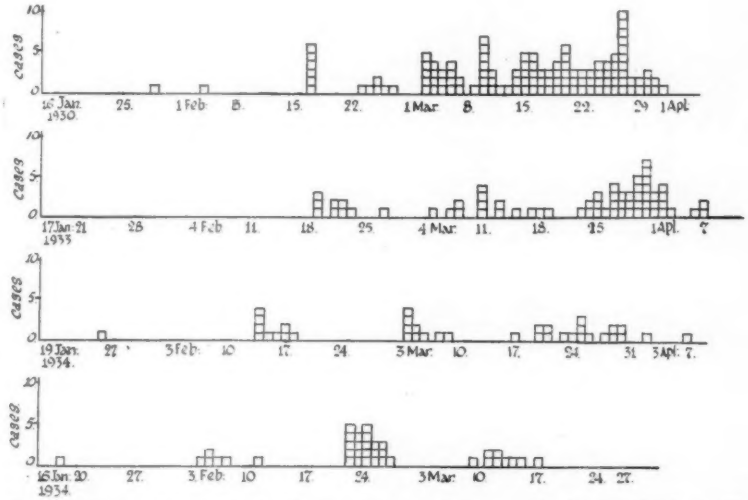


FIG. 1—Showing the daily incidence of cases of mumps in four epidemics. (From "Epidemics in Schools," Spec. Rep. Ser. Med. Res. Coun., 1938, No. 227, p. 161. Reproduced by permission of the Controller of H.M. Stationery Office.)

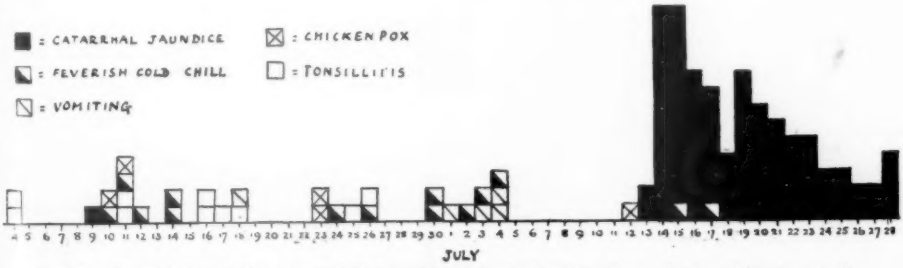


FIG. 2.—Catarrhal jaundice at a public boarding school, showing the explosive character of the epidemic. (*Lancet*, 1931 (i), 722. Reproduced by permission.)

showed three diagrams, the first (fig. 1) giving four typical daily incidence charts of school epidemics of mumps, a disease which has the same incubation period as the long incubation type of epidemic catarrhal jaundice. He pointed out the straggling incidence in all these epidemics (characteristic of a disease whose incubation period may vary by as much as a week) compared with the almost explosive incidence shown in the daily incidence chart (fig. 2) of the short

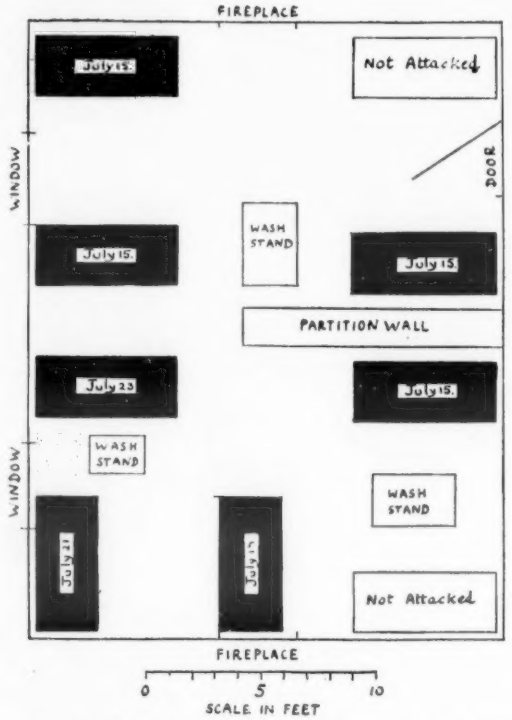


FIG. 3.—Plan of dormitory in which seven out of nine boys were attacked. From *Lancet*, 1934 (i), 724. (Reproduced by permission.)

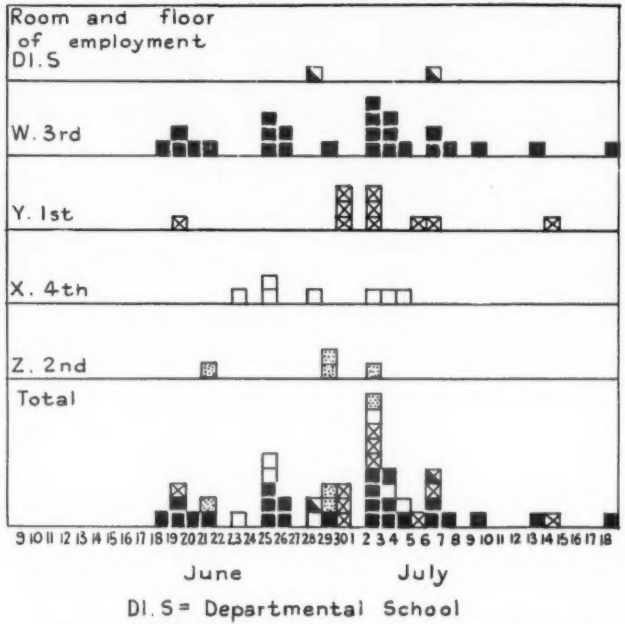


FIG. 4.—Epidemic of catarrhal jaundice in certain rooms at the General Post Office, June-July, 1934. (From Tables by H. H. Bashford, *Lancet*, 1934 (ii), 1008.)

period catarrhal jaundice epidemic described by Wilson and himself. The extreme steepness of the epidemic wave in the latter was much more like that of an influenza epidemic. The third diagram (fig. 3) showed the incidence in one dormitory during the same epidemic. Nine boys slept in the dormitory, seven of whom were attacked; in five cases the onset was on the same day, in the sixth there was an interval of six days, followed in two days' time by the seventh.

Dr. Glover also showed a chart of daily incidence by rooms, constructed from the details given by Sir Henry Bashford (fig. 4) of the epidemic of catarrhal jaundice at the General Post Office in 1934. Thus dissected, the incidence might be interpreted in favour of a short incubation period. The occurrence of missed cases and cases "sine eruptione" and the possibility of carriers in all epidemics, made the determination of incubation period exceedingly difficult.

There might be a third type, of which the extensive epidemic at Mount Allison University recorded by Roy Fraser [1] was an example. This epidemic was closely associated with an epidemic of gastro-enteritis due to a Salmonella infection.

Dr. J. M. ALSTON said that Dr. Cullinan spoke of vaccination for preventing leptospiral jaundice in people whose occupation or pursuits made them liable to this infection. He did not think the other means were worth consideration. The results of vaccination on a large scale in Japan were not clearly decisive in favour of it and there were some severe reactions to the vaccine. In this country, Dr. John Smith vaccinated some children and produced antibodies, but of a rather low titre. From another aspect among London sewer-men, who form one of the largest groups of men exposed to this risk in Great Britain, the morbidity rate is only 1% per annum, so that there must be some doubt whether the result of vaccination could justify the time, expense, and risk involved. In occupations in restricted premises, such as fish-curing, Dr. Alston said it would seem that good hygiene should banish the infection.

Dr. W. N. PICKLES said that instances of hepatic necrosis appeared in mild epidemics and seemed to have a common ætiology and incubation period. Close contact—e.g. sharing a bed—seemed to be a factor in the transference of infection. He showed a chart on the screen of a recent epidemic in his practice, which strengthened the evidence of a long incubation period.

He asked Dr. Cullinan if he had evidence of permanent damage to the liver in patients who had suffered from this disease.

Dr. G. M. FINDLAY said that until the causal agent or agents had been identified and isolated, there would continue to be uncertainty as to the number of conditions included under the designation of infective jaundice. One form of infective jaundice was undoubtedly associated with an acute hepatitis, and evidence recently obtained strongly suggested that this hepatitis was due to the action of a virus (Findlay, MacCallum and Murgatroyd, 1939). Following immunization against yellow fever, 95 cases of jaundice had been traced among 3,100 persons inoculated with an attenuated strain of yellow-fever virus grown in tissue culture. By eliminating various factors and finally by changing the strain of yellow-fever virus employed, this jaundice, which resembled in every way common infective hepatic jaundice, had now been eliminated and no case had occurred in more than 3,500 persons. Evidence suggested that the virus had been introduced into the tissue cultures with apparently normal serum. This was strictly analogous to the occurrence of jaundice following immunization against measles. In the jaundice following both measles and yellow-fever immunization, the incubation period had been longer than that usually associated with common infective hepatic jaundice. It must, however, be remembered that the incubation period of many virus infections, rabies for instance, showed very great variation, more especially when the virus was introduced by an abnormal route. Both the measles and yellow-fever jaundice cases had shown a tendency to be collected in little groups, but it was uncertain whether this was due to factors peculiar to a particular place or to random distribution of susceptible persons. One great difficulty in establishing the virus ætiology of infective hepatatis was the failure to infect a laboratory animal. Recently, however, it had been possible to obtain a febrile reaction in rhesus monkeys by feeding them by stomach tube with whole blood obtained

[1] *Canadian Pub. Health J.*, 1931, **22**, 396.

from cases of jaundice in the early stages. To establish whether this reaction in monkeys was due to a specific infection or not, blood from early further cases of jaundice was urgently required.

The view that jaundice was a contagious disease was of very long standing. Zacharias, who was Pope from A.D. 741 to 752, writing to St. Boniface in Germany, strongly recommended that patients with jaundice should be segregated lest others catch the contagion (cf. Migne: *Patrologia latina*, **89**, 951).

Reference.—FINDLAY, G. M., MACCALLUM, F. O., and MURGATROYD, F. (1939), *Tr. Roy. Soc. Trop. Med. & Hyg.*, **37**, 575.

Dr. J. W. HEALY said that with a view to learning more about the prevalence and clinical features of epidemic jaundice amongst children of school age in L.C.C. schools, residential schools, and special hospitals, at the beginning of last year district medical officers were asked to report on all children excluded from school on account of jaundice, on other children in the school suffering from the disease, and on the possible source of infection in each case. Later, this was further systematized by circulating a questionnaire to ascertain in addition the date of onset, clinical features, duration of illness, and hospitalization.

Over the period November 1937 to February 1939, 193 cases of jaundice were notified in this way. Some of the data, however, were unreliable, and many mild cases must have been missed. 70% of cases in the series could be linked up with some other or others in point of time, but incubation periods could not be worked out in day-school outbreaks where knowledge of the conditions and duration of contact was lacking. In one special hospital ten cases occurred in one ward, four crops following the primary case, and there were five intervals of 25–28 days, two of 32, one of 35, and one of 16 days.

The largest school group was in the Isle of Dogs, the first two cases occurring at the end of December 1937, and 22 more were strung out over the first three-quarters of 1938. Some irregular clustering of cases within a few days' interval was observed in this series, and there were two long gaps of six weeks each, possibly due to school holidays or to a missed case. In two of the smaller school epidemics all the recorded cases were close together in time, viz. five cases in three weeks in one instance, four cases in eleven days in the other; perhaps examples of the explosive type of epidemic, but complete information is lacking, and there probably were a number of missed cases.

In the Isle of Dogs series there were two groups of children attending the same school and living in the same house. In one of these the time intervals between successive cases were 30, 21, 29, 25, and 27 days, being sufficiently constant to individualize the group, the contact conditions being known and supporting Pickles' deduction that the period of infectivity is relatively short.

Dr. Healy went on to say that the most common symptoms of the pre-icteric stage were drowsiness, headache, and vomiting. In 76 returns the duration of this stage was stated, and in 90% of them it lay between one and eight days. In 12 instances the stage lasted only one day, in one it lasted thirteen days, while in three there was apparently no prodrome. In 46 returns the duration of jaundice was given. In two-thirds of these the limits lay between seven and twenty-one days, in four instances it lasted a month, and in one, six weeks.

The cases were mild and there were no deaths. 33 children, i.e. between one-fifth and one-sixth of the series, were admitted to hospital, the remainder were treated at home.

In about half of the cases (52) in which the period of absence from school could be ascertained, it lay between two and four weeks. The shortest periods of absence were two of seven days each and the longest three of three months each, although coincident chorea may have been partly responsible for the prolonged absence in one of those cases.

Section of Psychiatry

President—H. CRICHTON-MILLER, M.D.

[*March* 14, 1939]

The Significance of Anoxæmia in Modern Psychiatric Treatment

By J. H. QUASTEL

Director of Research, Cardiff City Mental Hospital

ABSTRACT.—Blood in its passage through the brain loses oxygen and glucose at relatively high rates, the amount of oxygen disappearing being approximately equivalent to the amount of glucose consumed, calculating on the basis that the sugar is completely oxidized. The respiratory quotient of brain *in vivo* is unity. These facts point to the dominance of carbohydrate oxidation in brain respiration *in vivo* and are similar to those found in studies of brain *in vitro*.

Various factors influence glucose oxidation in brain, e.g. changes in the ionic environment of the cells, vitamin B_1, or the presence of narcotics. The latter bring about inhibitions of glucose oxidation in brain tissue which may in most cases be shown to be reversible *in vitro*. Glucose is not only important for the maintenance of respiration of brain but for enabling certain synthetic processes to occur. One of these is the formation of acetylcholine whose physiological significance is now well known and whose synthesis seems to be confined to the nervous system. This synthesis depends not only on the presence of glucose but on that of oxygen. The influence of glucose has been observed also in investigations on cortical potentials.

An important feature of the nerve cell is its vulnerability to the lack of oxygen. Reversibility depends on the degree and duration of the anoxæmia.

During insulin shock treatment studies of brain *in vivo* show lowered oxygen consumption and glucose utilization, these depending on the degree of hypoglycæmia. In cardiazol treatment, *in vivo* studies show that the oxygen content of the blood may fall to 42%. During the convulsion there is a greatly lowered arterial and venous blood-flow through the brain and cerebral anæmia becomes a marked feature. In narcosis treatment both *in vitro* and *in vivo* studies show a diminished ability of the brain to consume oxygen.

It is suggested that the most significant facts to be taken into account are (1) the importance of glucose and oxygen for the metabolism and function of the nervous system, (2) the vulnerability and varying sensitivities of nerve cells to lack of oxygen and glucose, (3) the occurrence of varying degrees of cerebral anoxæmia in narcosis, insulin and cardiazol treatments.

RÉSUMÉ.—Pendant son passage par le cerveau le sang perd une proportion relativement élevée d'oxygène et de glucose, la quantité d'oxygène qui disparaît étant à peu près équivalente à celle de glucose utilisée, admettant que la glucose soit complètement oxidée. Le quotient respiratoire du cerveau *in vivo* égale 1. Ces faits indiquent la prédominance de l'oxidation de

l'hydrate de carbone dans la respiration du cerveau *in vivo*, et sont analogues à ceux découverts par des études du cerveau *in vitro*.

Plusieurs facteurs influencent l'oxidation de la glucose dans le cerveau, comme les changements du milieu ionique des cellules, la vitamine B_1 ou la présence de narcotiques. Ces derniers produisent une inhibition de l'oxidation de la glucose dans le cerveau, qui, dans la plupart des cas, d'après des expériences *in vitro*, se trouve être réversible. La glucose est importante non seulement pour maintenir la respiration du cerveau, mais aussi pour rendre possible certains procès synthétiques, entre autres la formation de l'acétylcholine, dont l'importance physiologique est aujourd'hui reconnue, et qui semble être formée exclusivement dans le système nerveux. L'influence de la glucose a aussi été observée dans des études sur les potentiels corticaux.

Une caractéristique importante de la cellule nerveuse est sa vulnérabilité par le manque d'oxygène. La réversibilité dépend du degré et de la durée de l'anoxémie.

Des études *in vivo* du cerveau pendant le traitement par le choc insulinique montrent une diminution de l'utilisation de la glucose et de l'oxygène qui dépend du degré d'hypoglycémie. Pendant le traitement au cardiazol des études *in vivo* on démontré que le taux d'oxygène sanguin peut tomber jusqu'à 42%. Pendant la convulsion la circulation artérielle et veineuse dans le cerveau est beaucoup diminuée, et il survient une anémie cérébrale prononcée. Pendant le traitement par la narcose des expériences *in vivo* et *in vitro* ont démontré que le pouvoir du cerveau d'utiliser l'oxygène est diminué.

L'auteur suggère que les faits les plus importants à considérer sont, 1° l'importance de la glucose et de l'oxygène dans le métabolisme et les fonctions du système nerveux, 2° la vulnérabilité et les différents degrés de sensibilité des cellules nerveuses au manque d'oxygène et de glucose, et 3° l'existence de différents degrés d'anoxémie cérébrale pendant les traitements par la narcose, par l'insuline et par le cardiazol.

ZUSAMMENFASSUNG.—Während der Durchströmung des Gehirnes verliert das Blut verhältnissmässig rasch Sauerstoff und Glucose, wobei die Menge des verschwundenen Sauerstoffs ungefähr der Menge der verbrauchten Glucose entspricht, wenn man annimt dass der Zucker vollständig oxydiert wird. Der respiratorische Quotient des Gehirnes *in vivo* ist 1. Diese Tatsachen weisen auf das Überwiegen der Kohlehydratverbrennung bei der Atmung des Gehirnes *in vivo* hin, und gleichen den Verhältnissen wie sie bei *in vitro* Untersuchungen des Gehirnes gefunden wurden.

Verschiedene Faktoren beeinflussen die Oxydation der Glucose im Gehirn, z.B. Veränderungen im Ionenmilieu der Zellen, Vitamin B_1 oder die Anwesenheit von Schlafmitteln. Letztere verursachen eine Hemmung der Glucoseoxydation im Hirngewebe, die sich *in vitro* in den meisten Fällen als reversibel nachweisen lässt. Die Glucose ist nicht nur für die Erhaltung der Atmung des Gehirnes wesentlich, sondern ermöglicht auch den Ablauf gewisser synthetischer Vorgänge. Zu diesen gehört die Bildung von Azetylcholin, dessen physiologische Bedeutung heute allgemein bekannt ist, und dessen Synthese auf das Zentralnervensystem beschränkt zu sein scheint. Diese Synthese ist nicht nur an die Anwesenheit von Glucose, sondern auch an die von Sauerstoff gebunden. Der Einfluss der Glucose ist auch bei Untersuchungen über die kortikalen Potentiale beobachtet worden.

Eine wesentliche Eigenschaft der Nervenzelle ist ihre Empfindlichkeit gegenüber Sauerstoffmangel. Die Reversibilität der Schädigung hängt von dem Grad und der Dauer der Anoxämie ab.

In vivo Untersuchungen des Gehirnes bei Insulinshockbehandlung zeigen eine dem Grade der Hypoglykämie entsprechende Verminderung des Sauerstoff- und Glucoseverbrauches. *In vivo* Untersuchungen bei Kardiazolbehandlung zeigen dass der Sauerstoffgehalt des Blutes auf 42% fallen kann. Während des Krampfes ist der Blutstrom durch die Arterien und Venen des Gehirnes stark vermindert, und es kommt zu deutlicher Hirnanämie. Bei Narkosebehandlung zeigen sowohl *in vitro* als auch *in vivo* Untersuchungen eine Herabsetzung der Fähigkeit des Gehirnes Sauerstoff zu verbrauchen.

Es wird darauf hingewiesen dass die wichtigsten in Betracht zu ziehenden Tatsachen die folgenden sind : 1. Die Bedeutung der Glucose und des Sauerstoffs für den Stoffwechsel und die Funktion des Nervensystems, 2. die Verletzbarkeit und wechselnde Empfindlichkeit der Nervenzellen gegenüber Sauerstoff- und Glucosemangel, 3. das Vorkommen von Anoxämie verschiedenen Grades bei der Narkose-, Insulin- und Kardiazolbehandlung.

THE oxygen content of blood leaving the human brain is, according to Lennox (1936), less than that of blood leaving the face or the extremities. Blood in the internal jugular vein contains oxygen to the extent of 61·5% of the saturation value, whereas the oxygen content of blood in the external jugular vein is 87% of the saturation value. It is well known that the grey matter of brain has a high rate of oxygen consumption. The actual amount of oxygen consumed seems to be approximately 8 ml. per 100 ml. of blood in its passage through the human brain. Now Myerson and Halloran (1930, 1931) and Lennox (1931) have shown that blood on passing through the brain loses carbohydrate, the difference between the glucose contents of arterial and cerebral venous blood (9–10 mgm.%) being greater than that (5 mgm.%) between the glucose contents of arterial and muscle venous blood.

If we take the value 10 mgm. per 100 ml. blood to be a roughly accurate measure of the glucose consumption of human brain *in vivo* the amount of oxygen required to burn this amount of glucose completely to CO_2 and H_2O would be 7·5 ml.%, agreeing fairly closely with the fall in oxygen content of 100 ml. blood in its passage through the brain. From the experiments of Himwich and Fazekas (1937) the loss of glucose in blood passing through the brain of an anæsthetized dog is 13 mgm.% corresponding to an oxygen consumption of 9·7 ml. per 100 ml. blood—assuming complete oxidation of glucose. They found the average difference between the oxygen contents of arterial and cerebral venous blood to be 9·3 ml.%.

It seems highly probable from facts such as these that glucose oxidation is the dominant respiratory process of brain *in vivo*. This is borne out by measurements of the respiratory quotient. Lennox arrived at an average respiratory quotient of 0·95 for human brain on the basis of a large number of experiments, and a respiratory quotient of unity has been found also with dog's brain.

Investigations of isolated brain tissue show also the importance of glucose oxidation as a major metabolic process in the central nervous system. This is shown in Table I. Thin slices of brain cortex are used in these experiments, as little damage as possible being done to the brain in the process of slicing. The respiration of such slices in a suitable physiological medium in an atmosphere of oxygen is low unless a metabolite is present in the medium. Much experience has shown that glucose, and its breakdown products, lactic and pyruvic acids, are the most satisfactory metabolites for securing and maintaining the respiration of brain *in vitro* at a high and constant value.

TABLE I.

Brain cortex slices	Medium	Qo_2 O_2 consumed by 1 mgm. dry weight tissue per hour	Reference
Rat	Ringer	3·9	Dickens and Greville (1933)
	Ringer-Glucose ..	12·8	
Rat	Phosphate-Locke ..	2·9	Jowett and Quastel (1937)
	Phosphate-Locke-Glucose	12·2	

The respiratory quotient of brain cortex slices *in vitro* is approximately unity (Dickens and Greville, 1933 ; Dickens, 1936) and it has been shown that the amount of glucose disappearing aerobically in the presence of brain slices is equal to that expected from the oxygen consumption of the tissue, assuming complete oxidation of the sugar (K. C. Dixon, 1936).

All the facts, therefore, obtained in the study of brain both by *in vivo* and by *in vitro* methods show the dependence of brain respiration on the supply of glucose. Glucose, just as much as oxygen, is essential for normal brain respiration. Lack of glucose will create in the brain a state equivalent to anoxæmia[1] even if oxygen is present, for the latter element will not be utilized. Similarly, if conditions obtain

[1] The term "anoxæmia" will therefore be used rather loosely to denote not only a state characterized by lack of oxygen but a state in which oxidative reactions are suppressed even if oxygen be freely available.

which prevent the oxidation of glucose by the brain cell, either through lack of oxygen or by other means, a state of anoxæmia will develop.

Various important factors influence glucose oxidation in the brain, as for example the ionic environment of the cell, or the presence of vitamin B_1 which is now well known from the work of Peters and his colleagues to be necessary for the oxidation of a breakdown product of glucose, pyruvic acid. It is also known that narcotics have the property of inhibiting measurably the oxidation of glucose at concentrations which secure narcosis. The effects of luminal (Jowett and Quastel, 1937) on rat-brain cortex respiration are shown in Table II.

TABLE II.

Substrate	Qo_2 without narcotic	% inhibition of respiration found when in presence of 0·08% luminal
Nil	2·89	5
Glucose	12·20	55
d.Lactate ..	13·55	35
Pyruvate	11·10	27
Glutamate ..	8·03	15
Succinate ..	9·53	0

The greatest effect of the narcotic lies with glucose oxidation, and the effect is usually reversible (Quastel and Wheatley, 1934). Ether, however, speedily brings about irreversible effects in *in vitro* investigations. The data in Table III (Jowett, 1938) show that a definite inhibition of brain cortex respiration takes place at concentrations of narcotics of the order producing deep narcosis. It appears probable from these results that narcotics bring about suppressions of oxygen utilization in those parts of the nervous system where they are adsorbed owing to their interference with the oxidation of glucose at the nervous centre in question. It has to be borne in mind that the inhibition of glucose oxidation to be expected during narcosis, as a mean effect spread over the whole of the grey matter of the cerebral cortex, is not necessarily large. The effects may be localized, greater inhibitions being experienced in certain parts of the brain than in others.

A number of amines, known to have marked effects on the nervous system, e.g. mescaline, bulbocapnine, also have inhibitory effects on the oxidation of glucose by brain.

Glucose is not only important for the maintenance of respiration of brain but for enabling certain synthetic processes to take place. A most important process is the formation of acetylcholine, whose physiological significance is now well known and whose synthesis seems to be confined to the nervous system (Quastel, Tennenbaum, and Wheatley, 1936; Mann, Tennenbaum and Quastel, 1938).

TABLE III.

Narcotic	Animal	Narcotic concentration, m	% inhibition of brain cortex respiration due to the narcotizing concentration of narcotic
Ethyl urethane	Rat	0·022	6
Mg ion	Rabbit	0·005	12
Mg ion	Rat	0·005	13
Chloral hydrate	Rat	0·0013	10
Luminal	Rat	0·00079	15
Chloretone	Rat	0·001	20
Evipan	Guinea-pig	0·00062	17
Avertin	Rat	0·00106	31
Chloretone	Guinea-pig	0·0010	32

This synthesis depends not only on the presence of glucose but on that of oxygen. The synthesis is greatly influenced by the ionic environment of the cell and, as in the case of respiration, the formation of acetylcholine is secured to the greatest extent by glucose or its breakdown products, lactic or pyruvic acids. This has been confirmed by McIntosh (1938) in perfusion experiments with ganglia.

The influence of glucose has been observed also in investigations of cortical potentials. The abolition of brain potentials in anoxæmia has been shown by Davis, Davis and Thompson (1938) and by Hoagland (1938), and the changes of brain potential due to abrupt and complete stoppage of blood-flow and its release have also been investigated (Sugar and Gerard, 1938).

The presence of luminal slows the rate of cortical waves (Gibbs, Gibbs and Lennox, 1937), and it has been shown (Hoagland *et al.*, 1937) that in insulin hypoglycæmia there is a marked change in the nature of the cortical potentials and that electrical activity may cease if the hypoglycæmia is prolonged. Maddock, Hawkins and Holmes (1939) have shown that the frequency of cortical potentials becomes lower with fall of blood-sugar and that at low levels of blood-sugar the waves may disappear. The administration of glucose results in the restoration of the original rhythm after an interval depending apparently on the severity and duration of the preceding hypoglycæmia and on the dose of glucose administered (*see also* Moruzzi, 1938).

These facts, which have been so briefly considered, all point to the profound influence of glucose oxidation in brain metabolism and function.

An important feature of the nerve cell which must now be briefly considered is its vulnerability to lack of oxygen. An interruption of cerebral circulation for 6 to 8 seconds will produce loss of consciousness. The usual action potentials in the cat's cortex are obliterated by a cerebral anæmia of 20 seconds (Simpson and Derbyshire, 1934) and an anæmia varying from 2 to 15 minutes frequently causes irreversible changes in the cerebral cortex and medulla. Experiments by Heymans and Bouckaert (1935), in which the circulation of dogs is completely stopped and after various intervals re-initiated show that oxygen lack longer than five minutes results in the cessation of cerebral function, but that within this interval recovery is possible except for blindness. McFarland *et al.* (1937) consider that a decreased efficiency of eye movements can be used to detect early effects of oxygen deprivation. Little work has been done on brain *in vitro* on the effects of oxygen lack, but what has been accomplished is in accordance with the results found *in vivo*. Brain respiration and metabolism have been found to be much influenced by exposure to oxygen lack and reversibility depends on the degree and duration of the anoxia.

In particular it may be mentioned that acetylcholine formation by intact brain slices under optimal respiratory conditions is greatly decreased by previous exposure of the slices either to lack of glucose or to lack of oxygen. The former condition has apparently the more harmful effects. The decrease may be as great as 50% after previous exposure of the intact brain slices to pure nitrogen (in the presence of glucose), or to oxygen in the absence of glucose, for one hour at 37° (Mann, Tennenbaum and Quastel, unpublished).

The effects of mechanical damage on brain respiration in presence of glucose depends greatly on the part of the brain examined (Dixon and Meyer, 1936). The facts would indicate that brain cells, whilst sharing a common dependence on glucose oxidation, vary considerably in their sensitivities to oxygen lack, their abilities to recover from exposure to anoxæmic conditions, and in their vulnerabilities to mechanical damage.

Let us now consider the effects of insulin and cardiazol administration on metabolism in the central nervous system.

Dameshek, Myerson and Stephenson (1935) came to the conclusion that the consumption of glucose by the brain is materially reduced during a severe hypoglycæmic reaction following insulin administration, and that the utilization of oxygen by the brain becomes smaller the greater the degree of hypoglycæmia. Himwich and Fazekas (1937) have shown that the difference between the glucose contents of arterial and cerebral venous blood under intense hypoglycæmia is 3 mgm.% as compared with a normal difference of about 13 mgm.%. Moreover, the oxygen consumption of dog-brain *in vivo* falls from a normal average figure of 7·99 vols. %

to 3·80 vols. % during intense hypoglycæmia. Some of their figures are shown in Table IV.

TABLE IV.

	O_2			Glucose mgm.%		
	Arterial*	Venous*	Difference	Arterial	Venous	Difference
Normal	21·59	11·78	9·81	83	68	15
During hypoglycæmia ..	20·90	16·57	4·33	15	12	3

* Femoral artery and superior longitudinal sinuses.

According to Leibel and Hall (1938) the blood-flow in the cerebral branch of the jugular vein increases at the onset of the primary convulsion after insulin treatment, and this is quickly followed by a considerable decrease in the rates of both arterial and venous flow. The cerebral blood-flow may be decreased to as low as 25% of the normal value.

It must be concluded that a suppression of oxidative systems develops in the central nervous system during the intense hypoglycæmia following insulin administration even though oxygen may be available as indicated by the relatively high oxygen content of the cerebral venous blood.

So far as *in vitro* work is concerned it is known that the respiration of the brain of an animal killed after it has been allowed to convulse after insulin administration is less than that of the brain of a normal animal, the brain tissues being examined in glucose-free media (Holmes, 1930). This is due to the fact that such a brain has been nearly completely depleted of glucose. Wortis (1935) has shown that the brain of an insulin-treated animal respires normally in a glucose medium. The isolated brains of insulin-treated or diabetic animals burn glucose at normal rates, and it is evident that the presence or absence of insulin does not affect the ability of the brain to burn glucose. Only so far as the availability of glucose to the nervous system is concerned does insulin appear to affect its carbohydrate oxidation.

Turning to cardiazol treatment, it has now been found (Himwich *et al.*, 1937) that the content of oxygen of arterial [1] blood falls during the convulsions, and it is reported that the saturation of the blood may be below 50% towards the end of the seizure. When the convulsion is completed the anoxæmia is evidenced by a pronounced cyanosis. The convulsions cause a temporary but marked depression of cerebral functions as shown by amnesia, confusion, and disorientation. Presumably the changes in function may be attributed to the anoxæmia. According to Leibel and Hall (1938) the blood-flow changes in cardiazol treatment are even more pronounced than in those following insulin administration. The decrease in cerebral flow, arterial and venous, is sufficient to produce a severe and prolonged cerebral anoxæmia.

Histopathological studies in brain after cardiazol treatment (Strecke *et al.*, 1938) show that the cerebral damage is greater the longer or more severe the intensity of the reaction.

Goodwin, Lloyd and Hall (1938), considering the effects of shock treatment on cortical potentials, state that the most conspicuous similarity between the actions of cardiazol and insulin is the prolonged phase of random slow-wave production which may be correlated with the period of reduced cerebral blood-flow and coma.

Cardiazol, as with insulin, has no effect on glucose metabolism of brain *in vitro* (Wortis, 1938).

So far as narcosis treatment is concerned Dameshek, Myerson and Loman (1934) have shown that in the human subject under the influence of amytal there is a small but definite inhibition of oxygen uptake and of dextrose utilization by the brain. The *in vitro* studies which have been considered make it most likely that local, if not general, suppressions of oxidation take place in the central nervous system.

[1] Femoral artery.

It will be observed that there is one feature common to narcosis, insulin, and cardiazol shock therapies: an interference with the respiratory metabolism of the central nervous system. Is this feature a purely fortuitous one, or can we assume that events do take place in the nervous system during a period of relative anoxæmia which will account for the increase rates of remissions effected by these treatments? It is evident that we have not yet sufficient information to allow us to put forward a satisfactory theory which will account for all the facts. Gellhorn (1938) considers that during anoxæmia a lasting stimulation of the sympathetic nervous system takes place and that this counteracts the parasympathetic reactions of the schizophrenic. Even if this were true it is difficult to see how it can account for the beneficial effects of narcosis treatment in manic-depressive cases. Jackson and Jackson (1938) believe that the fundamental event is a rise in blood-pressure resulting in the opening up of fresh brain capillaries and so oxygenating previously oxygen-deficient areas of the central nervous system. If this view represented the whole truth it would have been thought possible that treatment with adrenaline or ephedrine might be as efficient as the shock treatment.

It is difficult at first sight to see how a treatment which must create a relatively great disturbance in the metabolism of the central nervous system can have beneficial rather than harmful effects. It has to be borne in mind, however, that the exposures to lowered oxidative metabolism are short in duration and reversibility of cell function is possible for the short intervals involved. In narcosis treatment large falls of oxidative metabolism do not occur, and perhaps it is for this reason that a lengthy duration of treatment is necessary. It is, however, a distinguishing feature of the nerve cell that it is highly vulnerable to oxygen or glucose lack and that susceptibility varies greatly in the nervous system. Is it possible that during the periods of lowered oxidative metabolism certain nerve cells are destroyed or made inactive and that among these are cells or processes which, in cases of mental disorder, may have contributed materially to those disturbances which resulted in the abnormal mental manifestations?

The dominant facts, as I see them, are:—

(1) The demand by the brain for a continuous supply of oxygen and of glucose for its normal metabolism and function.

(2) The vulnerability and varying sensitivities of nerve cells to oxygen and glucose lack.

(3) The occurrence of varying degrees of anoxæmia in narcosis, insulin, and cardiazol treatments.

It is not too much to hope that experimental investigations based upon these facts may lead to fresh developments in therapy and to new light being thrown on the causes of mental disorder.

REFERENCES

Dameshek, W., Myerson, A., and Loman (1934), *Am. J. Psychiat.*, **91**, 113.
Dameshek, W., Myerson, A., and Stephenson (1935), *Arch Neurol. & Psychiat.*, **33**, 1.
Davis, P. A., Davis, H., and Thompson, J. W. (1938), *Am. J. Physiol.*, **123**, 51.
Dickens, F. (1936), *Biochem. J.*, **30**, 661.
Dickens, F., and Greville, G. D. (1933), *ibid.*, **27**, 832.
Dixon, K. C. (1936), *ibid.*, **30**, 1479.
Dixon, T. F., and Meyer, A. (1936), *ibid.*, **30**, 1577.
Gellhorn, E. (1938), *Arch. Neurol. & Psychiat.*, **40**, 125.
Gibbs, F. A., Gibbs, E. L., and Lennox, W. G. (1937), *Tr. Am. J. Neurol.*, **63**, 129.
Goodwin, J. E., Lloyd, D. P. C., and Hall, G. E. (1938), *Proc. Soc. Exper. Biol. & Med.*, **38**, 897.
Heymans, C., and Bouckaert, J. J. (1935), *Compt. rend. Soc. de biol.*, **119**, 324.
Himwich, H. E., and Fazekas, J. F. (1937), *Endocrinology*, **21**, 800.
Himwich, H. E., Bowman, K. M., Fazekas, J. F., and Orenstein, L. L. (1937), *Proc. Soc. Exper. Biol. & Med.*, **37**, 359.
Hoagland, H. (1938), *Am. J. Physiol.*, **123**, 102.

HOAGLAND, H., RUBIN, M. A., and CAMERON, E. E. (1937), *ibid.*, **120**, 559.
HOLMES, E. G. (1930), *Biochem. J.*, **24**, 914.
JACKSON, D. E., and JACKSON, H. L. (1938), *J. Lab. & Clin. Med.*, **23**, 1240.
JOWETT, M. (1938), *J. Physiol.*, **92**, 322.
JOWETT, M., and QUASTEL, J. H. (1937), *Biochem. J.*, **31**, 565.
LEIBEL, B. S., and HALL, G. E. (1938), *Proc. Soc. Exper. Biol. & Med.*, **38**, 984.
LENNOX, W. G. (1931), *Arch. Neurol. & Psychiat.*, **26**, 719.
Id. (1936), *ibid.*, **36**, 375.
MADDOCK, HAWKINS and HOLMES, E. G. (1939), *Am. J. Physiol.* In the press.
MANN, P. J. G., TENNENBAUM, M., and QUASTEL, J. H. (1938), *Biochem. J.*, **32**, 253.
MCFARLAND, R. A., KNEHR, C. H., and BERENS, C. (1937), *Am. J. Ophthal.*, **20**, 1204.
MCINTOSH (1938), *J. Physiol.*, **93**, 46 P.
MORUZZI (1938), *Compt. rend. Soc. de biol.*, **128**, 1181.
MYERSON, A., and HALLORAN, R. D. (1930), *Am. J. Psychiat.*, **10**, 389.
Id. (1931), *Bull. Massachusetts Dept. Ment. Dis.*, **15**, 9.
QUASTEL, J. H., and WHEATLEY, A. H. M. (1934), *Biochem. J.*, **28**, 1521.
QUASTEL, J. H., TENNENBAUM, M., and WHEATLEY, A. H. M. (1936), *ibid.*, **30**, 1668.
SIMPSON, H. N., and DERBYSHIRE, A. J. (1934), *Am. J. Physiol.*, **109**, 99.
STRECKE, (1938), *Tr. Am. Neurol. A.*, p. 10.
SUGAR, O., and GERARD, R. W. (1938), *J. Neurol.*, **1**, 558.
WORTIS (1935), *Arch. Neurol. Psychiat.*, **33**, 1022.
Id. (1938), *New York State J. Med.*, **38**, 1015.

Coma Resistance and Adrenalæmia in the Insulin Treatment of Schizophrenia

By M. S. JONES, M.R.C.P.E.

(*From the Maudsley Hospital, London*)

WHILE treating schizophrenic patients by the induction of hypoglycæmic coma with insulin, I have been interested in the enormous individual variation to the dose of insulin required. Some patients have had satisfactory comas with 36 units, while others have shown no clouding of consciousness with 300 units.

The existence of "insulin-resistant" cases of diabetes mellitus has long been recognized (Lawrence, 1928; Root, 1929).

Himsworth (1936) considers that diabetics can be divided into an insulin-sensitive type and an insulin-insensitive type. These two types are differentiated on the basis of an insulin-sensitivity test, which is carried out by comparing a routine glucose tolerance curve with the curve following the administration of a certain dose of insulin intravenously to the fasting patient together with a glucose drink. In the insulin-sensitive group the insulin considerably depresses the level of the blood-sugar, and the curve given by glucose + insulin is lower than that given by glucose alone, while in the insulin-insensitive group the normal glucose tolerance curve is not appreciably lowered by the addition of the small amount of insulin intravenously. Himsworth believes that insulin insensitivity is due to the lack of an unknown factor which sensitizes the body to insulin. In brief, Himsworth believes that not all cases of diabetes are due to lack of insulin, but that some, the insulin-insensitive group, might be due to a lack of the sensitizing factor in the presence of normal amounts of insulin.

De Wesselow and Griffiths (1938) could find no evidence for the existence of two distinct types of diabetic patient, and found that it was possible, by means of carbohydrate and insulin, to convert a diabetic from the insulin-resistant to the insulin-sensitive state. They (1936) believe, however, that the sera of certain elderly obese glycosuric patients have the property of inhibiting the fall of blood-sugar which occurs normally after the intravenous injection of 0·2 unit of insulin into the rabbit. In this respect the sera behaved similarly to extracts of anterior pituitary gland.

Young (1936) has described a "glycotrophic" factor present in anterior pituitary lobe extracts which abolishes the hypoglycæmic action of 2 units of insulin given intravenously to the fasting rabbit: this effect could also be demonstrated in the adrenalectomized animal, which suggests that the glycotrophic factor does not produce its effect through stimulation of adrenaline from the adrenals. This is important, because Cope and Marks (1934) have suggested that the insulin resistance of the pituitary injected animal might be due to the liver glycogen stores becoming unusually susceptible to the mobilizing action of adrenaline, so that the development of hypoglycæmia is prevented by the increased production of glucose by the liver.

Cases which result from undoubted overactivity of the anterior pituitary, e.g. acromegaly and Cushing's syndrome, and are associated with hyperglycæmia, show an insulin-insensitive type of response to the insulin-sensitivity test (De Wesselow and Griffiths, 1938; Flaum, 1938).

It is apparent from the foregoing remarks that very little is yet known about insulin resistance, and certainly there is no conclusive proof that an insulin-antagonistic substance can be demonstrated in the blood or urine of insulin insensitive diabetics, acromegalics, or cases of basophil adenoma of the pituitary.

Little has been done in studying cases with a normal glucose tolerance but who demonstrate an excessive insulin resistance. Hall (1938) describes a case undergoing insulin shock treatment, in which the initial injection of 20 units of insulin caused the blood-sugar to fall from 88 to 70 mgm.% in two hours, but who developed such a resistance to insulin that a coma could not be obtained: 1,000 units of insulin given in one injection reduced her blood-sugar from 115 to 80 mgm.% in two hours, while the serum showed a definite ability to inactivate insulin.

We have found several cases in which 300 units of insulin have been unsuccessful in inducing a deep coma after four to five hours, and have studied two such cases in some detail.

The first case is a boy aged 15 whose schizophrenic illness dates from nine months ago. Pubic hair appeared at the age of 10 and erections a year later. He started to shave when aged 13, and now does so every week. The penis and testicles are those of a well-developed adult, and the legs are extremely hairy. Other findings are a normal basal metabolic rate, negative Wassermann reaction, normal eye grounds, absence of glycosuria or ketonuria, and on X-ray examination the pituitary fossa was found to be very shallow and the anterior clinoid processes almost non-existent. The appearance was slightly suggestive of pressure from above, and in front of this area, though there was no evidence of actual bone erosion. The glucose tolerance after 50 grm. of glucose by mouth was, fasting, 88 mgm.%, and half-hourly estimations up to three hours show 95, 129, 134, 117, 106, and 106 mgm%. An insulin-sensitivity test, performed by giving the same amount of glucose plus 5 units of insulin intravenously, showed no significant drop when compared with the glucose tolerance test. The figures were: fasting, 84 mgm.%; after 10 minutes, 90 mgm.%; after 20 minutes, 90 mgm.%; after 30 minutes, 106 mgm.%; after 45 minutes, 113 mgm.%; after 55 minutes, 113 mgm.%; after 70 minutes, 110 mgm.%; after 85 minutes, 120 mgm.%; and after 100 minutes, 110 mgm.%.

He has shown no clouding of consciousness or loss of ability to do calculations after 300 units of insulin, although sweating and increase of pulse-rate, respirations, and blood-pressure, occur. After 100 units of insulin the blood-sugar fell to 56 mgm.% after two hours. After 300 units of insulin the lowest figure found has been 38 mgm.%, but four hours after the injection of 300 units of insulin the figure is usually over 40 mgm.%. On the evidence furnished by the insulin-sensitivity test and the hypoglycæmic response to large doses of insulin, it would appear that this patient shows some insulin insensitivity.

The clinical picture suggests the possibility of anterior pituitary overactivity, which might account for the insulin insensitivity. However, the basal metabolic rate was within normal limits, an assay of a forty-eight-hour specimen of his urine for gonadotrophic hormone showed that this was not present in excess (less than 20 rat units per litre of urine).

Fresh plasma showed no power to inhibit the hypoglycæmic action of 0·2 unit of insulin injected intravenously into the rabbit; the technique employed was similar to that described by Young (1936 *b*).

It is clear, therefore, that we were unable to obtain any indication as to the nature of the insulin resistance in this case, but the possibility of a pituitary or adrenal antagonist cannot be entirely excluded.

The second case, a male schizophrenic aged 24, showed no significant physical findings. His basal metabolic rate was normal, X-ray of the skull showed no abnormality, and there was no evidence of endocrinopathy.

A glucose tolerance test after taking 50 grm. of glucose by mouth showed fasting level 106 mgm.%, and half-hourly figures up to three hours were 124, 150, 130, 104, 99, and 84 mgm.%. With the insulin sensitivity test a marked sensitivity to insulin was shown. The fasting level was 70 mgm.%, and then at ten-minute intervals up to one hour the figures were 63, 52, 45, 34, 48, and 48 mgm.%, then rising to the original fasting level in two hours.

Blood-sugar curves after the injection of 100, 200, and 300 units of insulin gave very similar figures, the smaller doses giving, if anything, lower readings.

The lowest figure recorded at any time with this patient during hypoglycæmia was 18 mgm.%.

In spite of the fact that this patient showed no evidence of insulin insensitivity and gave a hypoglycæmic response to insulin comparable with cases in which coma was easily induced, he proved to be extremely "coma-resistant". A deep coma was never achieved, and although he had 60 treatment days on 300 units of insulin, he was usually fully responsive at the end of four hours hypoglycæmia.

The problem here is not one of insulin insensitivity but an anomalous response of the central nervous system to hypoglycæmia. It seems necessary to distinguish such "coma-resistant" cases from "insulin-resistant" cases.

We now went on to consider, in a more general way, to what extent the adrenaline response to hypoglycæmia varies in different cases, and whether this might in itself be a factor in the prevention of coma. Cannon *et al.* (1924) have shown that hypoglycæmia calls forth an outpouring of adrenaline and mobilization of liver glycogen. Stewart and Rogoff (1916) state that splanchnic stimulation, continued over many hours, does not result in a failure of adrenaline secretion. Theoretically it might be possible to demonstrate this adrenaline-hyperglycæmic mechanism in any one of three ways: (1) indirectly by clinical observation, noting the occurrence of such evidences of sympathetic activity as increase of pulse-rate and blood-pressure, increased respirations, and dilatation of the pupils, (2) by frequent blood-sugar determinations, (3) by an attempt to measure the blood adrenaline.

(1) Ten cases were followed continuously from the time of giving the usual coma dose of insulin until two hours had elapsed. There is a definite and constant pattern of reaction in the early stages of hypoglycæmia. The pulse-rate, blood-pressure, and respiration rate, change usually within a few minutes of each other, the whole occurring approximately 30 to 60 minutes after the insulin injection. The pulse and respiration rate quicken appreciably, while the blood-pressure shows an increased pulse-pressure, changing from, say, 118/87 to 148/60. This sudden alteration occurs when the blood-sugar has dropped to below 60 mgm.%, the range in this series being 38 to 59 mgm.%. No significant alteration in the size of the pupil was noted up to the time of onset of the above physiological changes, and on only two occasions did sweating start during this period.

These changes do not necessarily result from a sudden outpouring of adrenaline from the adrenals; as a control, 0·05 mgm. of adrenaline was injected intravenously into several cases in the early stages of hypoglycæmia, the result being a sudden rise of pulse-rate and blood-pressure, the response occurring immediately, and conditions returning to the pre-injection level within three to six minutes in the

five cases studied. In this type of response the blood-pressure rises suddenly from, say, 132/60 to 162/90 with no increase of pulse-pressure as occurs in the physiological response to hypoglycæmia.

However, previous studies of the blood-pressure response to subcutaneous injections (Jones, 1935) showed that when adrenaline is absorbed slowly in this manner, there is a tendency for the diastolic blood-pressure to fall, along with a rise of systolic blood-pressure. In other words, the increased pulse-pressure found in hypoglycæmic cases may result from adrenalæmia.

(2) In eight cases blood-sugars were taken at intervals of five to ten minutes after the injection of the usual coma dose of insulin, the pulse, respirations, and blood-pressure, being recorded continuously by a second investigator. When the blood-pressure, pulse-rate, and respirations rose, blood samples were taken as quickly as possible, i.e. at two to five minute intervals. No constant rise in blood-sugar was found to accompany the physiological change, but in four of the eight cases a definite rise of blood-sugar occurred twenty to forty minutes after the onset of the physiological response to the hypoglycæmia ; the rises were from 39 to 66 mgm.%, from 48 to 63 mgm.%, from 36 to 56 mgm.%, and from 38 to 59 mgm.%.

It is thus apparent that any reactionary rise of blood-sugar which may occur does so some considerable time after the onset of increased blood-pressure, &c.

The effect of the injection of 0·05 mgm. of adrenaline intravenously was now observed in five cases, the injection being given two and a half to three hours after the administration of the coma dose of insulin, i.e. when the patient was almost in coma. In three cases there was no rise in blood-sugar at all ; in the other two cases the rise was 34 to 95 mgm.% in six minutes, and 67 to 85 mgm.% in ten minutes.

However, when 0·5 mgm. of adrenaline was given subcutaneously to five cases at a similar stage of the hypoglycæmia, a steady rise of from 15 to 32 mgm.% was obtained in all cases within a period of forty minutes after the injection. This tendency for adrenaline to have less action in raising the blood-sugar when given intravenously than when given subcutaneously is well recognized (Grollmann, 1936).

Our results suggest that the response of the blood-pressure, respirations, pulse-rate, and blood-sugar to hypoglycæmia bear no close relationship to the responses obtained by the injection of intravenous adrenaline to the hypoglycæmic patient, but are somewhat similar to the response obtained when adrenaline is injected subcutaneously during hypoglycæmia. However, much further work is needed to establish this point.

(3) There are many difficulties in attempting to assay the blood adrenaline directly The biological method most frequently used for these determinations is open to many objections and the pressor response measured may not be wholly attributable to the adrenaline. In the living animal, Elliott (1905) found that 1 mgm. of adrenaline was inactivated by the liver in seven minutes, and Rogoff and Marcus (1938) state that when 25 to 50 times the normal output of the dog's adrenal per minute is given in a single injection, only 25% to 50% of the adrenaline may be detected in arterial blood one minute after the injection, while rarely could any adrenaline reaction be detected after two minutes. However, when large amounts of adrenaline were injected at a constant rate for an hour or longer, a small reaction was occasionally observed as long as twenty minutes after the end of the injection.

From these remarks it would appear that if adrenaline is released as a sudden outpouring when a certain hypoglycæmic threshold is reached, then any attempt to obtain a sample of arterial blood during the period of two minutes before the adrenaline is inactivated by the tissues is liable to fail.

Dr. Derek Richter has kindly assayed the adrenaline content of venous and arterial blood during the period when, as a result of developing hypoglycæmia, the blood-pressure, pulse-rate, and respirations, have been raised above the initial level.

The method used was the chemical method developed by Whitehorn (1934) and Shaw (1938), depending on selective adsorption and reduction of an arseno-molybdate reagent. This method is an improvement on previous chemical methods, being more specific for adrenaline and more sensitive. Its sensitivity is comparable with physiological methods.

Six determinations were made on arterial blood removed during the period of physiological response to the hypoglycæmia, and these were controlled by six determinations on venous blood removed after treatment. The figures obtained ranged from 1·5 to 5·9 parts per 100,000,000, with a mean of 3·4 parts per 100,000,000, for arterial blood, and 0 to 3·8 parts per 100,000,000, with a mean of 2·5 parts per 100,000,000, for venous blood. This difference between arterial and venous blood is probably not significant.

It cannot be taken as certain that these figures represent the adrenaline content of the blood, as other unknown reducing substances of this type may be present in blood, but the figures do show that the adrenaline content cannot be significantly higher than the figures given. It is impossible to give normal figures for blood adrenaline, as the methods available are all open to criticism, and it is not definitely established that adrenaline is present in measurable quantities in the general circulation.

0·05 mgm. of adrenaline was given intravenously to a patient in coma, a needle having been previously inserted into the femoral artery, and 10 c.c. of arterial blood was removed immediately after giving the adrenaline injection: this blood sample gave a reading of 2·9 parts in 100,000,000, as compared with a control of venous blood taken after the completion of treatment, which gave a reading of 2·3 parts per 100,000,000. Although such a dose of adrenaline given intravenously has a very definite effect on the patient's physiological condition, it really represents a very high dilution in the patient's blood; if one assumes a blood volume of 5 litres, then the adrenaline is diluted 1 part in 1,000,000,000 and the method used gives definite readings at a dilution of about 1 part in 10,000,000. Similarly, 1·0 mgm. of adrenaline given subcutaneously did not cause a significant rise in the blood adrenaline figure, even though the blood-pressure rose from 120/80 to 180/90, at which time the sample of the arterial blood was obtained. The figures for arterial and venous blood were the same: 2·9 parts per 100,000,000.

In brief, all attempts to obtain a sample of arterial blood in which adrenaline was present in significantly high concentration, either as a result of the physiological response to hypoglycæmia, or to injected subcutaneous or intravenous adrenaline, proved unsuccessful.

To summarize, a case showing normal glucose tolerance, which is insulin resistant judged by the insulin-sensitivity test and hypoglycæmic response to large doses of insulin, is described. In this case there is no definite evidence of anterior pituitary overactivity, and no evidence of "glycotrophic" activity in the blood.

A second case, not insulin resistant, and showing marked hypoglycæmia in response to large doses of insulin but demonstrating "coma-resistance", is described.

No definite conclusion was formed as to the occurrence of an adrenaline response to hypoglycæmia during insulin treatment, but if this does occur, it appears to be more in the nature of a prolonged adrenaline hypersecretion than a sudden outpouring of adrenaline from the adrenals.

Adrenaline was not found in significantly high concentration in arterial blood when the clinical picture suggested the possibility of an adrenaline response to the developing hypoglycæmia.

[I wish to express my indebtedness to Dr. A. Walters, Dr. D. Richter, Mr. W. T. S. Smith, and Mr. A. H. Tingey, for much help in this study.]

REFERENCES

CANNON, W. B., MCIVER, M. A., and BLISS, S. W. (1924), *Am. J. Physiol.*, **69**, 46.
COPE, O., and MARKS, H. P. (1934), *J. Physiol.*, **83**, 157.
DE WESSELOW, O. L. V., and GRIFFITHS, W. J. (1938), *Quart. J. Med.*, **7**, 17.
Id. (1936), *Lancet* (i), 991.
FLAUM, G. (1938), *Endocrinology*, **23**, 630.
GROLLMANN, A. (1936), " The Adrenals ". London, p. 131.
HALL, G. E. (1938), *Am. J. Psychiat.*, **95**, 553.
HIMSWORTH, H. P. (1936), *Lancet* (i), 127.
JONES, M. S. (1936), *J. Ment. Sc.*, **82**, 785.
LAWRENCE, R. D. (1928), *Quart. J. Med.*, **21**, 359.
ROGOFF, J. M., and MARCUS, E. (1938), *J.A.M.A.*, **110**, 2127.
ROOT, H. H. (1929), *New England J. Med.*, **201**, 201.
SHAW, F. H. (1938), *Biochem. J.*, **32**, 19.
STEWART, G. N., and ROGOFF, J. M. (1916), *J. Pharmacol. & Exper. Therap.*, **8**, 479.
WHITEHORN, J. C. (1934), *J. Biol. Chem.*, **108**, 633.
YOUNG, F. G. (1936*a*), *Lancet* (ii), 237 and 297.
Id. (1936*b*), *J. Physiol.*, **87**, 13P.

Dr W. D. Nicol: The problem of schizophrenia as presented by Dr. Quastel is one of anoxaemia—the dominant facts as he sees them are (1) the demand by the brain for a continuous supply of oxygen and glucose for its normal metabolism and function and (2) the vulnerability and varying sensitivities of nerve cells to oxygen and glucose lack.

This deficiency of oxidative processes is not a new theory; it was postulated as long ago as 1909 by Koch and Mann [1], in their investigation of neutral sulphur.

In 1919 Haldane [2] delivered a lecture on the symptoms, causes and prevention of anoxæmia, which he defined as " a condition in which the rate of supply of oxygen to the tissues by the blood in the systemic capillaries is insufficient for the normal carrying on of life ". The clinical effects of anoxæmia on the nervous system are characteristic—to quote this article " the senses become dulled without persons being aware of it, and if the anoxæmia is suddenly relieved by administration of oxygen or other means the correspondingly sudden increase in powers of vision and hearing is an intense surprise. Powers of memory are greatly affected, and are finally almost annulled, so that persons who have never lost consciousness can nevertheless remember nothing of what has happened. Powers of sane judgment are much impaired, and anoxæmic persons become subject to fixed ideas which afterwards appear to them quite irrational, and to unrestrained emotional outbursts ".

I have risked quoting this clinical description at length because it brings out quite clearly that lack of oxygen in the brain is accompanied by mental symptoms, a fact of which perhaps some of us are unaware. The anoxæmic symptoms described above are immediately relieved by restoring an adequate supply of oxygen. Dr. Quastel himself uses the term anoxæmia somewhat loosely and states that it " denotes not only a state characterized by lack of oxygen but a state in which oxidative reactions are suppressed even if oxygen is freely available." Unfortunately the solution of the anoxæmia of the schizophrenic is not so simple. Loevenhart, Lorenz and Waters [3] in their studies on schizophrenic cases reported that lucid intervals varying from 4 to 20 minutes in catatonic patients could be produced by the administration of high percentages of carbon dioxide and oxygen. This lucidity followed a reaction resembling the fourth stage of anæsthesia. Subsequently Hinsie, Barach and others [4] had schizophrenics living in a converted dormitory for six weeks, during which the oxygen content of the atmosphere was raised to 45–50% and carbon dioxide only to 2–4%, but in all these patients no clinical changes of consequence were observed at any time following the cessation of treatment. Here it must be noted that in these second experiments the element of shock was eliminated. One suggestion put forward by Dr. Quastel is that the nervous tissues are unable to use the oxygen brought to them by the blood—this would correspond to the histotoxic

anoxæmia described by Hadfield and Garrod [5]. In this connexion it might be worth mentioning that Freeman [6] claims to have found a deficiency of catalytic iron in the brain of schizophrenics. Is it not possible, however, that a diminished consumption of oxygen in the schizophrenic might be due to the diminished requirements of the nervous cells in these patients for oxygen and not to any failure to utilize it.

Dr. Quastel puts forward as an alternative theory that " during periods of lowered oxidative metabolism certain nerve cells are destroyed or made inactive " whether in the course of hypoglycæmic shock or narcosis ; he asks whether these destructive processes have eliminated those cells which might have been responsible for the symptoms. It seems difficult to believe that any form of therapy could be so conveniently selective. It must, however, be generally conceded that deficient oxidation in the brain occurs in schizophrenia and extensive researches have been carried out showing the relationship between the respiration and the metabolism of the brain. Yet it would appear that the schizophrenic makes little effort to remedy his lack of oxidation ; on the contrary he shows a tendency to acidosis, shallow respiration is evident (as has been shown by Golla [7] and his co-workers), the thin pulse is not suggestive of increased circulation and on those rare occasions that one can see an autopsy during this disease process, the heart is fibroid, ill-nourished and almost infantile in size.

Dr. Goodall [8] in his Presidential Address to this Section in 1937 made a plea for team work in attacking these problems ; he deplored the fact that biochemical research in connexion with mental disorders is prosecuted in so few laboratories.

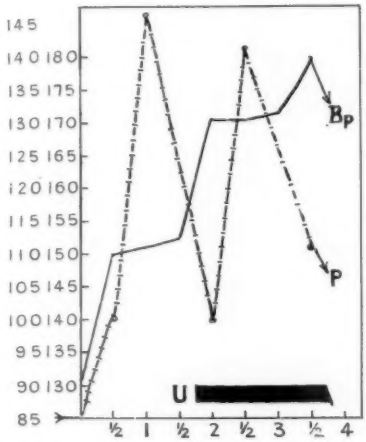
These biochemical researches seem to spell chaos to the clinician, yet our own inexact methods must be equally confusing to the chemist. Only by patient research and by means of sifting scientific evidence by collaboration with the scientist can we hope to build up the foundations on which we can interpret this intricate neuropathology with all its inexplicable symptomatology.

REFERENCES

1 Koch, W., and Mann, S. A., A chemical study of the brain in healthy and diseased conditions, with especial reference to dementia præcox, *Arch. Neurol. & Psychiat.*, 1909, **4**, 174–219.
2 Haldane, J. S., The symptoms, causes and prevention of anoxæmia, *Brit. M. J.*, 1919 (ii), 65.
3 Loevenhart, A. S., Lorenz, W. F., and Waters, R. M., Cerebral Stimulation, *J.A.M.A.*, 1929, **13**, 880–883.
4 Hinsie, L. E., Barach, A. L., Harris, M. M., Brand, E., McFarland, A., Treatment by continuous oxygen administration and oxygen and carbon dioxide inhalations, *Psychiatric Quart.*, 1934, **8**, 34.
5 Hadfield, G., and Garrod, L. P., " Recent Advances in Pathology ". Churchill, 1932.
6 Freeman, W., Deficiency of catalytic iron in the brain in schizophrenia. " Assocn. for Research in Nervous and Mental Disease ", Vol. X. Baltimore.
7 Golla, F. L., Mann, S. A., and March, H., The respiratory regulation in psychotic subjects, *J. Ment. Sc.*, 1928, **74**, 443.
8 Goodall, E., Physical research in psychiatry, *Proc. Roy. Soc. Med.*, **13**, Part I, 49.

Dr. Francis Reitmann: The assumption that cerebral anoxia was the final agency in producing the results of shock therapy suggested trying the effect of anoxæmia induced directly by low oxygen supply. Dr. R. Fraser and myself undertook experiments on these lines at the Maudsley Hospital. Patients were made to inhale a mixture of 2% oxygen and nitrogen under normal atmospheric pressure. In the course of these investigations, which could not be pursued to a definite therapeutic result, some interesting observations on the clinical picture of pure anoxæmia were made which I should like to mention here, as the uncomplicated picture is not very widely known, and as it permits the drawing of some interesting comparison with the cardiazol fit.

The diagram demonstrates the cardiovascular symptoms. The blood-pressure rises, the pulse-rate increases very irregularly, the respiration becomes more frequent. The patient's cyanosis is visible in the film. During the unconsciousness marked in the diagram by a black bar, the pupils are wide and do not respond to light. The most significant difference between the anoxic and the cardiazol effects was the complete absence of epileptiform fits from the former. Differences in the motor symptoms will be seen in the film. The vascular responses are very similar, though even there some differences could be found. Pulse-rate and blood-pressure returned to normal more rapidly after the termination of the anoxia than recovery from the cardiazol fit, and no irregularities of the pulse were seen.



The clinical comparison suggests the conclusion that cardiazol produces some other important changes that cannot be produced by severe anoxia of similar duration —most particularly evident in the production of an epileptiform fit. Therefore, although the anoxia may play a part in the pathogenesis of cardiazol effects, it presumably cannot be regarded as the most important mechanism of its action. Even if the effects of anoxia and cardiazol are similar, it does not follow, of course, that anoxia is the pathogenetic basis of its action.

Dr. E. Guttmann showed a film illustrating the clinical picture of anoxæmia as produced by Dr. Fraser and Dr. Reitmann in experiments with inhalation of low oxygen mixtures. The same patient was filmed during a cardiazol convulsion ; the differences in the pattern of neurological response and the different speed of recovery were demonstrated.

Dr. E. L. Hutton : It is with great interest that I have listened to Dr. Quastel's paper to-night. The possible role of anoxæmia as a causative factor in schizophrenia is one that cannot lightly be ignored. When I first became interested in the subject I was fortunate enough to be allowed to study the mental symptoms produced by low atmospheric pressures. By the kind permission of the Air Ministry I was allowed to visit the experimental chamber at Farnborough, where the atmospheric pressure could be reduced so as to correspond with altitudes up to but not exceeding 54,000 ft.

I have here a few notes written by one of the occupants of the chamber when the atmospheric pressure corresponded to an altitude of 17,000 rising to 22,000 ft. I was breathing oxygen from a cylinder, but the writer was not. Both objectively and subjectively the clinical picture he produced was one of alcoholic intoxication. He was originally elated, said he felt like drinking champagne, he thought his own jokes inordinately funny, and he wanted to fight another occupant of the chamber who was about twice his own size. He had some insight into his condition and, like the alcoholic, would occasionally try to pull himself together. I think this alcoholic effect is also shown in the notes.

These visits to the experimental chamber very strongly impressed upon my mind the undoubted fact that anoxæmia does produce very obvious psychological disturbance.

At the same time my attention was drawn to certain similarities between the physical and mental states in sleep and schizophrenia, which have been noted and recorded by various observers [1]. Of particular interest were the changes which occur in the respiratory and circulatory systems in these two states. In both there have been recorded a lowering of the basal metabolic rate, a reduction of the air intake due to slower and shallower respiration, a decrease of the circulatory rate and output, alterations in the acid-base equilibrium, and finally changes indicative of increased tonus of the parasympathetic nervous system.

A hypothesis of auto-asphyxiation seemed to offer a possible explanation of the mechanism of sleep. Dr. Quastel has shown us to-night that the oxygen requirement of brain tissue is high, and it is not improbable that the more highly developed the cell, the greater its oxygen need. If by means of a gradually increasing parasympathetic tonus the oxygen intake could be slowly diminished, one would expect the brain cells gradually to cease functioning, the cessation of function occurring first in the most highly developed cells and then descending the scale until only the vital processes were left functioning. As the parasympathetic tonus waned the oxygen intake would again increase and the cells would resume their function in an ascending scale until full waking consciousness is restored.

As regards the schizophrenic it seemed feasible that in their desire to avoid a painful reality they might be making a perverted use of a physiological mechanism already to hand, whereby they are able to eliminate unpleasant thoughts and feelings by refusing to let their minds function normally. It seemed to me an attractive theory, and I was loth to abandon it. I myself sought to prove the existence of a deficient oxygen intake in the schizophrenic. The technical difficulties encountered deterred me from completing the work and publishing the results, but I convinced myself that there was no arterial anoxæmia, and this has been confirmed by the work of Hinsie *et al.* in 1934 [2].

In 1926 [3] Segal and Hinsie published a paper in which they note " the oxidation of the venous blood in the lungs of our patients was manifestly incomplete ". In 1934, however, it is stated that " the earlier studies of Segal and Hinsie are thus not confirmed. Even in the presence of considerable peripheral anoxæmia, the arterial oxygen saturation was found to be normal ; i.e. the cyanosis must be a variety of stagnant anoxæmia ".

What is the explanation of the respiratory changes in the schizophrenic ? The processes of cell metabolism and cell respiration are as yet but ill understood. The changes occurring in muscle, both during the resting and working phases, seem to have been studied most fully. One may be led into making grossly inaccurate assumptions if one supposes that the metabolic changes in nervous tissue are analogous to those occurring in other tissues, but as even the most highly developed cells trace back their family tree to the same undifferentiated protoplasm, is it unreasonable to suppose that family likenesses do exist ?

Now in muscle the liberation of energy which can be converted into work is due to the breakdown of glycogen into lactic acid and of phosphagen into creatine and phosphate. This is an anaerobic change and occurs in the entire absence of oxygen during the resting stage and to a more marked extent during contraction, but under normal conditions it is checked before all the available glycogen or phosphagen is used up. In this way the tissues are normally prevented from entirely depleting themselves of their store of potential energy. The aerobic phase is concerned entirely with the restitution of the normal store of potential energy, i.e. with the resynthesis of glycogen and phosphagen. By suitable means the cell can be induced to release more of its stored potential energy or can be prevented from releasing so much, but ultimately unless its stores are replenished it finally ceases to function at all.

Is it not possible that oxidative processes throughout the body serve not catabolic but anabolic changes? A. V. Hill [4] compared the activity of muscle with the function of an accumulator. The electrical energy which a charged accumulator delivers on closing the circuit originates in the end in the supply of energy in being charged. According to Hill, this charging up is being done in muscle during the recovery period when by the expenditure of oxygen potential energy is accumulated. May not this be true of nervous tissue also?

May we not consider sleep as a mechanism which has been evolved by the organism to prevent an excessive discharge of energy by the nervous accumulator, while providing suitable conditions for the recharging—and not only for the recharging but for the overhauling and reconditioning of the accumulator itself. If this is the case, any oxygen deficiency during sleep would defeat this object, and therefore on purely theoretical grounds becomes improbable.

Here I would repeat my suggestion that the schizophrenic is making a perverted use of the sleep mechanism; that he uses it to inhibit painful and unpleasant mental processes—he uses it to prevent the discharge of nervous energy—and if the accumulator is but little discharged, there is equally little need for recharging, i.e. equally little need for oxidation.

Meyerhof [5] writes: "In the work of muscle the explosive formation of lactic acid is the decisive event, while the removal of lactic acid means recovery. Now it is evidently easier to obtain an instantaneous effect by increasing a chemical effect which is already under way than first to set it going. Respiration at rest is subservient to the readiness for work. We may compare it to the state of a cranked motor car standing still!" Might we compare the schizophrenic to a driver whose previous driving experience has made him so apprehensive that he has tried to shut off his engine, and in some cases has throttled it down so successfully that it barely manages to tick over, and therefore later willy-nilly he cannot make the car go. In such a case, if the engine is violently cranked up and his fears of driving are removed by kindly advice and encouragment, this timid motorist may yet be able to make good use of his car. In the same way it is possible that shock therapy stimulates the retarded metabolism of the schizophrenic, while the subsequent psychotherapy, which has been found to be so useful an adjuvant, enables him to face with greater confidence the problems which led to his original breakdown.

In Dr. Quastel's experiments may not the anoxæmia found by him be the result of these violent metabolic changes induced by insulin and cardiazol, the principal factor being an excessive discharge of potential energy in the nervous system. If this be so, then the deficient aeration which occurs in schizophrenia and the altered oxygen consumption in insulin shock, cardiazol and narcosis are the results and not the causes of the physical and mental changes observed during this psychosis and its various methods of treatment. I should like to take this opportunity of thanking Group-Captain Struan Marshall for the assistance he has given me in these investigations on anoxæmia.

REFERENCES

1 Ewen, J. H., *J. Neurol. & Psychopath.*, Jan. 1934, **55**, 247–281.
2 Hinsie, E. E., Barach, A. L., Harris, M. M., Brand, E., McFarlane, A., *Psychiatric Quart.*, 1934.
3 Segal, L., Hinsie, L. E., *Am. J. M. Sc.*, 1926, **171**, 727.
4 Hill, A. V., quoted by O. Meyerhof, " Chemical Dynamics of Life Phenomena ".
5 Meyerhof, O., *ibid.*

Dr. J. H. Quastel (in reply) said : I have not ventured to make any statement in this paper to the effect that schizophrenia is characterized by anoxæmia in the nervous system, or that the latter condition is a causative factor in schizophrenia. I know of no decisive evidence which would lead to either of these conclusions, and the experimental difficulties in the way of securing such evidence are indeed great. It is, however, well known that an anoxæmia in the nervous system does lead to mental symptoms resembling those encountered among psychotic subjects, and it is a plausible view that some of the psychoses, themselves, may owe their origin to a deficient oxidative metabolism somewhere in the nervous system. Such a view, however, is far from proved, and must be considered at present purely as a working hypothesis. I have tried to show that the experimental evidence points to the dependence of brain, for its normal metabolism and function, on a continuous supply of oxygen and glucose, lack of either of these leads to changes in the nervous system which may become irreversible and the extent of which depends upon the period of anoxæmia or hypoglycæmia. Yet the treatment of mental disorder by narcosis, insulin, or cardiazol therapy, appears to have a common factor, the production of anoxæmia, or of a suppression of oxidations in the nervous system. This may be quite fortuitous. If the securing for a short time of a lowered oxidative metabolism in the nervous system leads to beneficial results in certain classes of psychotic patients, it would be expected that the exposure of such patients to atmospheres poor in oxygen might lead to equally beneficial results. The clinical picture obtained in this form of treatment may well differ from that observed in cardiazol or insulin " shock " treatment, for the mode of securing " anoxia " differs greatly. The important matter, however, is whether the form of treatment in question can lead to an improvement in the mental state. Experiments on lines similar to these should eventually yield sufficient evidence to enable us to decide whether the improvements effected by present-day psychiatric therapy are definitely associated with alterations in the oxidative metabolism of the nervous system.

Section of Urology

President—H. P. WINSBURY-WHITE, F.R.C.S.

[*February* 23, 1939]

The Treatment of the Incompletely Descended Testis

By D. S. POOLE WILSON, M.Ch.

ABSTRACT.—(1) Under three years of age the diagnosis of the incompletely descended testis is uncertain.

(2) The policy of awaiting spontaneous descent may be pursued until 10 years of age but, unless the testis lies in the superior scrotal position, this policy should not be persisted in thereafter.

(3) Hormonal therapy may be employed before operative treatment as a means of determining testes which will descend spontaneously. It should only be used in the prepuberty period.

(4) Operative treatment may be safely carried out at any age after 3 years and should be completed before puberty. The optimum period is between 8 and 11 years. The Bevan operation may be successful when the testis is very mobile but the most consistent results are obtained by the septal transposition or Keetley-Torek operations.

RÉSUMÉ.—(1) Avant l'âge de 3 ans le diagnostic de la descente incomplète du testicule est incertain.

(2) On peut attendre la descente spontanée jusqu'à l'âge de 10 ans, mais l'attente ne doit pas être continuée plus longtemps à moins que le testicule se trouve dans la position scrotale supérieure.

(3) Le traitement hormonal peut être employé avant l'intervention chirurgicale, pour découvrir les testicules qui descendront spontanément. Il ne doit être employé que pendant la période prépubérale.

(4) L'intervention chirurgicale peut être exécutée sans danger à n'importe quel âge après 3 ans, et devrait être complétée avant la puberté. Le meilleur âge est de 8 à 11 ans. L'opération de Bevan peut réussir si le testicule est très mobile, mais les succès les plus constants sont obtenus au moyen de la transposition septale ou de l'opération de Keetley-Torek.

ZUSAMMENFASSUNG.—1. Die Diagnose des unvollkommen herabgestiegenen Hodens bis ist zum Alter von 3 Jahren unsicher.

2. Bis zum zehnten Lebensjahre darf man auf das spontane Herabsteigen warten. Darüber hinaus sollte aber diese abwartende Behandlung nicht ausgedehnt werden, sofern der Hoden sich nicht in der oberen Hodensacklage befindet.

3. Hormonbehandlung kann vor der operativen Behandlung angewandt werden, u.zw. um herauszufinden, in welchen Fällen die Hoden spontan herabsteigen. Dieses Vorgehen empfiehlt sich aber nur in der Präpubertätszeit.

4. Nach Vollendung des dritten Lebensjahres kann die operative Behandlung zu jeder Zeit ohne Gefahr ausgeführt werden; sie sollte vor Eintritt der Pubertät abgeschlossen sein. Die beste Zeit ist die Altersstufe zwischen 8 und 11 Jahren. In Fällen, in denen die Hoden sehr verschieblich sind kann die Bevan'sche Operation erfolgreich sein, die besten Erfolge werden aber mit der septalen Transponierung oder der Keetley-Torek'schen Operation erzielt.

In 1899 when Bevan described his operation of orchidopexy he advised its performance immediately after puberty but suggested that advantages might be gained by operating at an earlier date. Within a few years he was advocating operation in early childhood and encountered considerable opposition to his views. The work of many surgeons and pathologists apparently substantiated his claims and the advantages of early operation appeared established. During the past few years, however, several papers have appeared in the English and American literature stressing the frequency of late descent of the testis and proposing delay of any operative procedures until after puberty. The use of gonadotrophic hormones as a means of inducing descent has also been introduced and far-reaching claims have been made for their efficiency.

At present there are, therefore, three methods of treatment at our disposal, firstly the policy of awaiting spontaneous descent, secondly hormonal therapy, and thirdly surgery. Opinions are at variance regarding the exact position of each procedure. In the present paper the treatment of 62 patients, representing 78 instances of incomplete descent, is considered, and an attempt made to review the principles of treatment in the light of the apparently stable facts regarding the pathology of the testis.

The external genitalia in normal children and adults show a wide range of development. Even so, if a large series of cryptorchids is observed, a small proportion of them will exhibit genitalia which are excessively diminutive. These children, in addition, commonly show either obesity, stunting of stature or other signs of hormonal deficiency. Many of them are suffering from dystrophia adiposa genitalis, or Fröhlich's syndrome. Their treatment lies entirely within the sphere of the physician and they have accordingly been excluded from this series, which deals only with incomplete descent of the testis occurring in the otherwise normal person.

Diagnosis and classification.—Arrest of the testis at any point in its normal path from the upper lumbar region to the scrotum constitutes incomplete descent. Usually the testis is present in the scrotum at birth, but in about 10% of full-term babies and more frequently in the premature the scrotum is empty. Descent may occur at any time during the first few years of life and it seems at least inadvisable to diagnose incomplete descent before a child is walking and perhaps before 3 years of age.

For the useful comparison of statistics the position of a testis must be accurately described. According to the point of retention it will fall into one of three groups :—

(1) Abdominal.
(2) Inguinal.
(3) Subinguinal. (*a*) Pubic.
(*b*) Superior scrotal.
(*c*) Superficial inguinal or ectopic.

The first two varieties refer to a testis retained in the abdomen or inguinal canal respectively. The subinguinal testis lies outside the external abdominal ring and three subgroups may be recognized, the pubic, the superior scrotal and the superficial inguinal testis. The latter variety, which is sometimes referred to as the inguinal ectopic testis, lies in the subcutaneous tissue upon the aponeurosis of the external oblique muscle. This is the position taken up by a testis, which, emerging from the external abdominal ring, finds the entrance to the scrotum closed.

From a clinical examination it is not always possible to place a testis in its exact category. The subinguinal testis may be recognized with certainty but its subgroups may not always be distinguishable. The inguinal testis is, however, rarely palpable and constitutes with the abdominal variety an impalpable group.

There are two further causes of inaccurate diagnosis. Firstly the presence of

large pads of fat in the suprapubic regions and groins of some young children, tends to make palpation difficult and renders the penis and scrotum diminutive in appearance. Secondly the cremaster muscle imparts a considerable range of movement to the testis. In childhood a temporary withdrawal into the inguinal canal may occur. Many of the inconsistencies in the literature appear to arise from confusion of this retractable type with the incompletely descended testis. The retraction may also cause an incompletely descended testis to appear of a more severe degree than its true nature. It is therefore essential that a testis should be graded by the lowest point to which it can be brought down and not by its resting position. By running the fingers down from the superior iliac spine to the external ring a previously impalpable testis may frequently be made to appear. Heat is also an invaluable prelude to palpation. Standing a boy with his trousers down for five to ten minutes before a hot fire or radiator will sometimes reveal what palpation has failed to demonstrate.

Two factors are of paramount importance in considering the treatment of incomplete descent :—

(1) The results of non-descent.

(2) The frequency of late spontaneous descent.

The results of non-descent.—John Hunter believed that the retained testis was imperfect and incapable of performing its natural functions. This conception has died hard. Curling, some fifty years after Hunter, concluded that the retained organ was not necessarily originally malformed. Odiorne and Simmons (1904), and Rawlings (1908) found that the incompletely descended testis in childhood showed no morphological changes but underwent none of the normal development of puberty. Southam and Cooper in 1928 examined a series of undescended testes removed at various ages and reported that the further the pre-adolescent testis has descended in its normal course and the younger the age at which it is examined the more closely does it correspond to the scrotal gland of the same age. At whatever position the testis is arrested and at whatever pre-adolescent age it is examined, the essential elements of the gland, spermatogonia and undifferentiated cells are, if not in all parts, certainly in many areas identical in position, structure and relationship with those of the corresponding scrotal organ. As puberty is approached various changes are noted, fibrosis occurs, and there is an apparent and actual disappearance of tubules, while the spermatogonia remain quiescent. The interstitial cells of Leydig, which are responsible for the internal secretion of the testis, are apparently not influenced by the abnormal situation of a retained testis.

Pace and Cabot (1936) have made a histological study of testes removed from 24 subjects, all of whom had passed puberty, and concluded that there is a suggestion of progressive degeneration as the years go by, so that apparently atrophy takes place and there is less likelihood of regeneration of the germinal epithelium, the longer the testes remain undescended.

Mimpriss has examined a series of testes removed from boys in the 10 to 14 age-period. All exhibited a histological picture of delayed development and had undergone no degenerative changes. The glands, which had been retained high up in the line of descent were, however, small in size. Specimens removed from older patients all showed degenerative changes in varying degrees.

Moore, experimenting on rats, guinea-pigs, dogs, rabbits, and sheep, found that if a testis was pushed into the abdomen and retained there by closure of the inguinal canal, the seminal epithelium degenerated but the interstitial tissue was unaffected. An appearance similar to the histological degeneration of the cryptorchid testis was obtained. There was also reason to attribute this destructive process to the increased temperature of the interior of the abdomen as compared with that of the scrotum. Moore further discovered that the degeneration of the seminal epithelium was

reversible and that if the testis were replaced in the scrotum its capacity for spermatogenesis would be retained. Wangensteen has conducted similar experiments with like results.

Despite the apparent non-degeneration of the interstitial cells the hormone content of the cryptorchid testis is lower than normal. Extracts of such testes are less potent and experiments on pig testes have shown that the cryptorchid organ contains about half the normal quantity of male hormone. This effect is also probably one of temperature.

These observations suggest that until puberty the undescended testis approximates to normal in structure but that subsequently degeneration occurs. It is certain that the testis for its full development requires a temperature slightly below that of the abdominal cavity.

To justify surgical procedures it is necessary not only to show that a retained testis atrophies but that development may occur following transference to the scrotum. Most of the investigations following orchidopexy have commented only on the position and subsequent development of the testes and for these there is no doubt that cosmetic results may be perfect. The occurrence of spermatogenesis is, however, the crucial test. The bilateral cryptorchid is usually considered sterile, though this is not invariable and cases of paternity have been recorded, amongst others by Marechal and Taylor, Schulz and Grey Turner.

The subject was first fully investigated by MacCollum, who examined 18 patients on whom bilateral orchidopexies had been performed. Six were married and had one or more children. Spermatozoa counts were also carried out and showed definite fertility in 11, potential fertility in three and complete absence of spermatozoa in four. A somewhat similar investigation was carried out by Wangensteen, who also examined tissue removed from testes during the first and second stages of a Keetley-Torek operation.

I have been unable to carry out investigations on the pathology of the retained testis. The necessity for castration practically never arises and I also consider it unjustified to remove a wedge of tissue at operation from a gland which one is endeavouring to save.

The frequency of late spontaneous descent.—There has always been a belief that descent of the retained testis may occur at puberty. Man's inherent dislike of disclosing deformities in the genitalia has made confirmation difficult and the wish has been suspected of fathering the thought. Thus Bevan (1929) maintained that spontaneous descent never occurs. Wangensteen (1927) believes that only rarely after the first year does the testicle reach the scrotum on its own inclination. Grey Turner (1937) has never been satisfied that descent occurs later than the age of 3 years. Other reports are not so pessimistic. Coley as long ago as 1908, observed that the frequency of incomplete descent diminished with advancing years. Pearse Williams examining 2,104 schoolboys found that 38 had one testicle undescended (1·8%) and 21 both testicles undescended (1%). Natural descent occurred about puberty in 24 (63%) of the unilateral cases and in 14 of the bilateral (64%). Drake also examining schoolboys found 11 cases amongst 260 boys (4·2%). Smith has observed spontaneous descent on 23 occasions. From these figures it will be seen that there are considerable differences in the reported incidence in childhood. The lowest estimate is probably that of Clement Dukes, who reported nine instances amongst 2,000 schoolboys (0·45%). Whichever figures, however, are accepted the incidence in childhood is considerably greater than the 0·25%, which is probably a maximum for the adult.

Mimpriss (1938) in reviewing a series of known cryptorchids found the testis in the scrotum on several occasions. In addition in a series of 31 personally observed children, at the time of writing, spontaneous descent had occurred in nine. Five of the children were 2 years of age or younger. The careful observations of

MacCollum, however, show a persistence of the condition in a high percentage of cases with final degeneration and atrophy of the testis. In addition some of the late descended testes are undeveloped and subsequently never reach normal proportions.

Two interesting examples of spontaneous descent have occurred amongst my own patients.

The first suffered from a left incompletely descended testis, which was noted at the age of 4 years. Being teased at school on account of his deformity he had from time to time examined himself carefully and was certain that although he could occasionally feel a swelling in the left groin, no testicle had ever appeared in the scrotum. At the age of 16 he attended an Officers' Training Corps camp and whilst engaged in physical training suddenly felt a severe sickening pain in his left groin. He was compelled to fall out of the ranks and returning to his tent found to his amazement two testes present in the scrotum. The testis has since never left the scrotum. It subsequently developed considerably but still remained smaller than its companion.

The second instance occurred in a boy (J. B.) aged 13 years who, when I examined him in 1935, was suffering from bilateral incompletely descended testes of the pubic type. The scrotum was poorly developed and there was no evidence of hernia. In May 1935 I performed a Keetley-Torek operation on the right side and returned the testis to the scrotum in January 1936. The boy failed to return for operation on the other side, but in reply to a letter, came to see me last August. The right testis was lying freely in the bottom of the scrotum and to my amazement the left testis was found lying at a somewhat higher level on the opposite side. It was smaller than its companion.

Various Forms of Treatment

I.—Awaiting Spontaneous Descent

Cabot has whimsically described this method as "watchful waiting". For the attainment of full development it is probably essential the testis should be in the scrotum by the onset of puberty. Inasmuch as pubescent changes become apparent as early as 11 years this is the latest date to which "watchful waiting" can be safely carried out. If proceeded with further spontaneous descent may occur but there is considerable risk that the testis may not subsequently develop and in the event of non-descent the chances of a successful orchidopexy are lessened. In the case of the superior scrotal testis some latitude may be allowed as it is the most likely to descend and the least likely to be damaged by atrophic changes. Except in this instance I do not, as yet, advise awaiting spontaneous descent beyond 10 years of age. This limit allows a period for hormonal or operative measures before the onset of puberty.

II.—Hormone Therapy

In 1930 Schapiro, using a gonadotrophic extract obtained from pregnancy urine, claimed to have obtained descent of the testis in a series of cryptorchids. Two years later Engle demonstrated that it was possible in the immature monkey, whose testes lie in the upper portion of the inguinal canal, to induce descent by similar means. These observations suggested a possible way of treating the incompletely descended testis and clinical trials were almost immediately commenced.

At first it seems strange that a hormone obtained from a pregnancy urine should have a masculinizing effect. Hypophysectomy in the male and female results in sexual non-development or atrophy. In the female the pituitary gland forms two gonadotrophic hormones, one responsible for maturation of the follicles and ovulation and a second responsible for luteinization. In the male two similar hormones are apparently secreted by the pituitary, the one activating the germ cells of the testes and controlling spermatogenesis, the other the interstitial cells and the production of testosterone. There is no reason to suppose that there is a pituitary sex difference, and extracts from male and female hypophyses appear to be inter-

changeable in respect of hormone production. Supplies of pituitary hormone are difficult to obtain and it is on this account that the gonadotrophic principle found in the urine of pregnant women is employed. This substance, discovered by Aschheim and Zondek in 1928, exerts similar effects to those produced by the anterior lobe of the pituitary.

At first extravagant claims were made for the efficacy of hormone therapy but latterly enthusiasm has become more restrained. Successful descent is claimed by various authors in from 20 to 50%.

During 1936–37 I treated with pregnyl a group of 17 boys suffering from incomplete descent of the testis. The dosage varied slightly from patient to patient, but usually consisted of 500 units administered twice weekly for ten weeks. The results are shown in Table I. Success was obtained in five patients,

TABLE I.—HORMONE THERAPY.

Patients, 17. Average age, 8 years.

Complete Descent .. .. .. 5 patients.
- Bilateral, 4 patients representing 7 testes.*
  - Pubic testes, 3.
  - Superior scrotal testes, 4.
- Unilateral, 1 patient.
  - Impalpable testis.

Improved .. .. 2 patients.
- Bilateral, 1 patient.
  - Superior scrotal testes, 2.
- Unilateral, 1 patient.
  - Pubic testis.

Failures .. .. 10 patients.
- Bilateral, 3 patients.
  - Impalpable testis, 1.
  - Pubic testis, 1.
  - Superficial inguinal testis, 2.
  - Superior scrotal testis, 2.
- Unilateral, 7 patients.
  - Impalpable testes, 2.
  - Pubic testes, 3.
  - Superficial inguinal testes, 1.
  - Superior scrotal testis, 1.

* A successful right orchidopexy had been performed on one patient.

approximately 30%, and occurred mainly in the bilateral and subinguinal varieties. In the two boys, who are improved, the testes are still retained in the superior scrotal position. In one of them the testis seems to be held up by a firm fibrous band. These boys are as yet only $6\frac{1}{2}$ and $7\frac{1}{2}$ years of age and it is possible that spontaneous descent may still occur. Of the ten failures all have had orchidopexies performed at periods varying from two months to four years after the cessation of treatment. In two of them the entrance to the scrotum appeared barred by fibrous tissue but in the other eight no exact primary cause of retention was determined.

Four children with retractile testes were also treated with pregnyl. In three the testes rapidly came to lie in the floor of the scrotum and in the fourth the affected testis was much less retractile.

Definite hypertrophy of the external genitalia was observed in seven boys and failure to descend occurred in six of them. Enlargement of the penis was the most prominent feature.

From experiments in rats it has been suggested by Evans and Mimpriss that atrophy of the testis may follow large doses of hormone. I have reviewed all my patients from time to time—14 of them have been seen during the past few weeks—

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 1.—A. G. Descent of the testes resulting from hormone therapy. The right testis was previously superior scrotal, and the left pubic in position.

FIG. 2.—L. B. Descent of bilateral pubic testes following hormone therapy.

FIG. 3.—S. G. Unilateral incomplete descent. The testis was impalpable. The penis hypertrophied but no descent followed treatment with hormones.

FIG. 4.—L. H. Bilateral incomplete descent. The right testis was pubic in position and the left impalpable.

FIG. 5.—L. H. Patient shown in fig. 4, after the administration of 9,000 units of pregnyl. The penis is hypertrophied but no descent has occurred.

and have seen no evidence of atrophy or non-development attributable to the treatment. In some of the unilateral cases the normal testis has enlarged during the period of treatment and regression has followed its cessation. None of these testes, however, show signs of permanent damage and all are developing normally.

Apart from the absence of testes from the scrotum, the external genitalia of the boys in my series were within normal limits. The hypertrophy of the genitalia, induced in some of them as the result of treatment suggests the production of an artificial puberty and it therefore seems probable that descent was obtained only with those testes, which would normally have undergone spontaneous descent at a later date. In the unilateral cases the presence of a normal testis in one-half of the scrotum is strong evidence that in these instances lack of pituitary hormone cannot be the cause of non-descent and that the defect must be mechanical. When descent, either spontaneous or produced by hormone therapy, occurs in these instances it must be the result either of enlargement of the testis facilitating the normal processes or the changes of puberty producing a general slackening of the tissues in the inguinal and scrotal regions.

From these observations it appears that the main function of hormone therapy should be to assist in determining the testes which will descend at puberty. It seems inadvisable to produce an artificial puberty in the very young and I therefore now delay treatment until 10 years of age. In the event of failure an orchidopexy may then be performed before the onset of puberty. Experience has shown that little hope of a satisfactory result can be entertained with the unilateral cryptorchid and I therefore hesitate to recommend this form of treatment to these patients.

III.—Operative Treatment

Three main procedures are usually described for the operative treatment of the imperfectly descended testis :—

(1) Orchidopexy or the transplantation of the testis to the scrotum.

(2) Replacement of the testis in the abdomen.

(3) Castration.

Operative treatment should in all cases aim at the replacement of the testis in the scrotum. If mobilization of an abdominal testis is impossible the gland may be left in the abdomen. Using two-stage operations if necessary, it should always be possible to bring down an inguinal testis. Castration should never be employed.

For an orchidopexy to be considered successful the testis must finally be mobile, lie in the floor of the scrotum and develop to normal dimensions. The multiplicity of operations described in the literature testifies to the difficulties experienced in attaining these criteria. The early operations concentrated on methods of fixation in the scrotum and proved uniformly disappointing. In 1899 Bevan opened a new era when he enunciated the principle that success primarily depends on the complete freeing of the testis, its vas and vessels ; and secondarily on adequate fixation of the testis in the scrotum. Bevan's method of fixation is probably now rarely employed but his description of the mobilization of the testis remains the most perfect in the literature and is the method which I have used.

Mobilization of the testis.—The inguinal canal is opened throughout its full extent as in a Bassini operation. The mobilization is carried out in four stages :—

(1) The processus vaginalis is divided close to the internal abdominal ring. Its proximal portion and the peritoneum of the posterior abdominal wall are separated from the anterior surface of the testicular vessels and the peritoneum closed.

(2) The testicular vessels are separated from the posterior abdominal wall.

(3) When these two processes have been carried out a fan-shaped band of fibrous tissue, in which the testicular vessels are contained, will be found extending from the cord upwards into the retroperitoneal region. These fibres are separated from the vessels and divided.

(4) When possible a tunica vaginalis is made and the remainder of the processus vaginalis removed. Any fibrous bands in the cord are divided.

In carrying out the operation it is frequently helpful to obtain better access to the retroperitoneal region by separating the origin of the internal oblique muscle from the inguinal ligament for a short distance. When these procedures have been completed the maximum amount of descent of the testis will have been obtained. The testicular vessels are certainly the barrier to further progress; shortness of the vas in my experience never gives rise to difficulty. The testicular vessels should never be divided as atrophy of the testis will certainly occur. Division of the deep epigastric artery has been recommended with a view to allowing the testicular vessels to take a more direct course from the aorta to the scrotum. Little can be hoped for by this means as the vessels must circumnavigate the pelvis and never take a really direct course. In addition I am in agreement with Dennis Brown that it is the medial margin of the internal abdominal ring rather than the deep epigastric vessels which

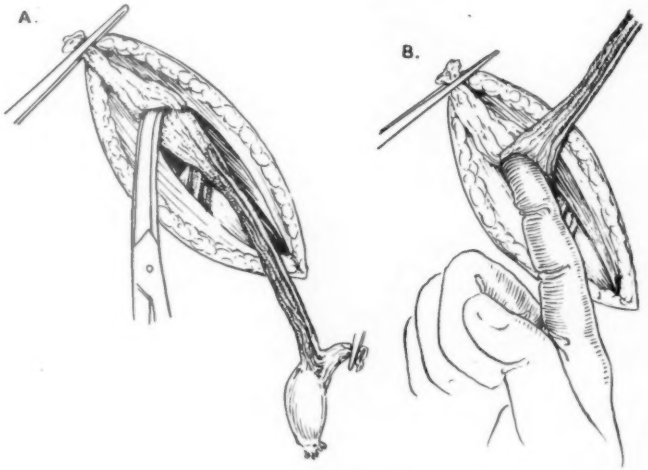


FIG. 6.—A, Mobilization of the testis. Separation of the processus vaginalis and peritoneum from the anterior surfaces of the testicular vessels and vas deferens. B, Separation of the testicular vessels and vas from the post-abdominal wall.

holds the vessels laterally. The interfoveolar ligament strengthens this portion of the fascia tranversalis and can easily be demonstrated at operation. It is divided in the course of the mobilization of the testis.

Fixation of the testis in the scrotum.—There are three useful methods of fixation of the testis in the scrotum. Their technique has been admirably described by McCrea.

(1) *The Bevan operation*: In this operation a bed is made for the testis in the corresponding half of the scrotum. Retraction of the testis is prevented by a purse-string suture inserted into the subcutaneous tissues so as to close the neck of the scrotum but not to embrace the cord. This technique is now seldom used and it is more usual to prevent retraction by passing a silkworm-gut stitch through the remains of the gubernaculum testis or the tunica vaginalis and having brought the ends out through the bottom of the scrotum to tie them over a piece of rubber tubing.

If more tension is required the stitch may either be sewn to the thigh or attached to it by strapping.

(2) *Septal transposition*: The compartment of the opposite half of the scrotum is opened by a low transverse incision. A small opening is then made in the septum and the mobilized testis is drawn through into the opposite half of the scrotum. The opening is closed snugly around the cord by one or two catgut sutures and the scrotal wound repaired.

(3) *The Keetley-Torek operation*: The testis is transplanted through the scrotum into the upper part of the thigh, where it is attached to the deep fascia. It is maintained in this position for three to six months so that lengthening of the cord is obtained and is then transferred back to the scrotum.

TABLE II.—OPERATIVE TREATMENT OF INCOMPLETE DESCENT OF THE TESTIS.

55 patients submitted to operation representing 66 retained testes.

Patients operated upon over six months ago :—
46 patients representing 55 orchidopexies.
44 patients representing 51 orchidopexies have been reviewed.

Bevan's operation.			
Success	4	Inguinal testis	1
		Superior scrotal testis	2
		Superficial inguinal testis	1
Improved	2	Superior scrotal testis	1
		Pubic testis	1
Failed	3	Inguinal testis	1
		Pubic testis	2
Septal transposition.			
Success	25	Abdominal testis	2
		Inguinal testis	5
		Pubic testis	10
		Superficial inguinal	4
		Superior scrotal	3
		Not classified	1
Improved	5	Inguinal testis	1
		Pubic testis	2
		Superficial inguinal testis	1
		Superior scrotal testis	1
Failed	5	Inguinal testis	3
		Pubic testis	1
		Superficial inguinal	1
Keetley-Torek operation.			
Success	6	Pubic testis	2
		Superficial inguinal testis	3
		Superior scrotal testis	1
Failed	1	Inguinal testis	1

In my series of patients I have used all three methods of fixation and the results are shown in Table II. The poor statistical reports of various authors on the Bevan operation and my own somewhat unsatisfactory results rapidly led me to abandon this method. When carrying it out I usually introduce a silkworm-gut traction stitch between the remains of the gubernaculum testis or the tunica vaginalis and the thigh. The practice of passing the stitch through the testis itself must be condemned on account of the likelihood of causing testicular destruction. The stitch is removed in ten to fourteen days. This period of traction seems insufficient as the testis, probably as the result of scrotal contraction, frequently drew up into the upper scrotum or pubic region and became fixed. Very careful nursing attention is required to keep the tension stitch continually taut and the child must be kept lying down. I would advise using this method only when the testis, following mobilization, can be placed without any tension whatsoever in the bottom of the

scrotum. This criterion is in my experience rarely achieved. It must, however, be admitted that Barrington-Ward using this method has published very satisfactory results.

Fixation by the method of septal transposition has been strongly advocated by Ombrédanne and has in my experience proved most satisfactory. The embrasure of the spermatic cord by the scrotal septum puts a barrier between the testis and its normal pathway. Considerable retraction of the testis may occur and the septum may be drawn up towards the pubic region but adhesions do not form between the testis and its old bed. The testis subsequently gradually descends and comes to

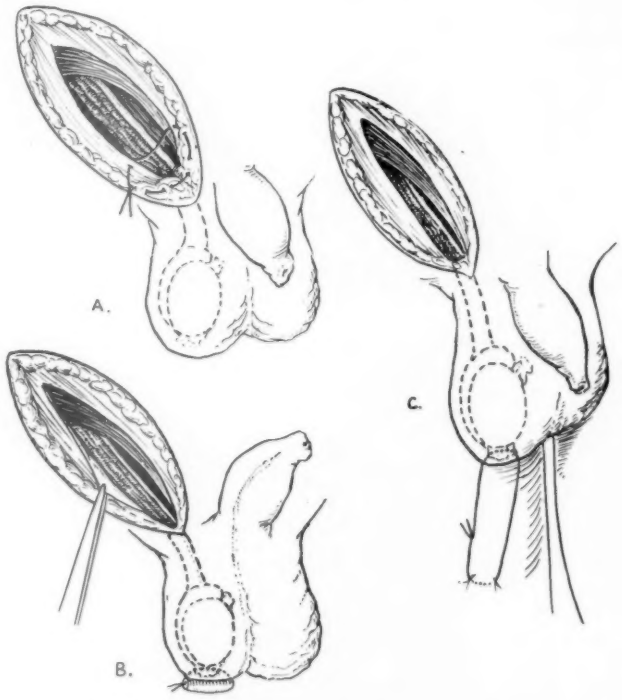


FIG. 7.—The Bevan operation. A, Bevan's original method of fixation. B, Attachment of remains of gubernaculum or tunica vaginalis to floor of scrotum. C, Tension stitch attached to thigh.

lie free in the floor of the opposite half of the scrotum. In carrying out this operation I have always found it an advantage to insert the stitches for the closure of the opening in the septum before the testis is drawn through, as if the testis is not very mobile the septum may be drawn up considerably and subsequent insertion becomes extremely difficult. The scrotal wound occasionally shows a tendency to become adherent to the testis but this can be easily avoided if the dartos muscle is approximated by fine catgut stitches. An eversion stitch should also be used for the skin. I am convinced that this operation may be successfully carried out in cases where fixation by the Keetley-Torek operation would be impossible and a

FIG. 8.—C. E. Successful Bevan operation. The right testis was held down by a stitch to the thigh. The left testis, which was operated on by another surgeon, was fixed to the bottom of the scrotum.

FIG. 9.—R. F. Bevan operation. The left testis is mobile but not at as low a level as its companion.

FIG. 10.—F. C. Bevan operation. An imperfect result. The right testis is held up towards the neck of the scrotum.

hree or more stage operation necessary. The main disadvantage of the method is hat the two testes come to lie in the same half of the scrotum and this necessarily

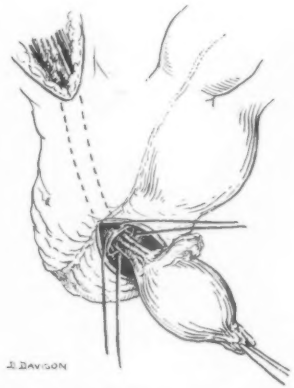


FIG. 11.—The septal transposition or Ombrédanne operation.

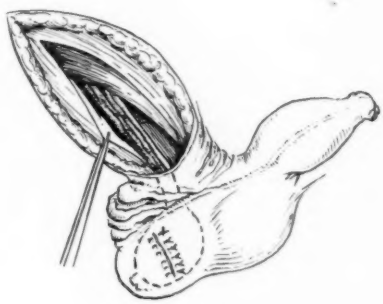


FIG. 12.—Showing how retraction of the fixed testis may draw the septum up to the affected side.

FIG. 13.—B. H. Successful septal transposition of the right testis. The testis is lying low down in the left half of the scrotum.

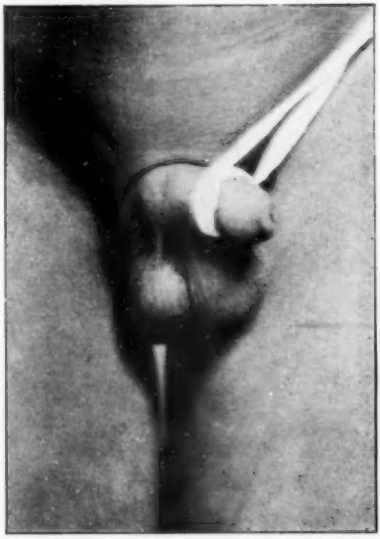


FIG. 14.—B. H. Patient shown in fig. 13, taken two years later. The scrotum has now assumed a more symmetrical appearance.

gives rise to some asymmetry. With the passage of time this, however, becomes less marked and is not in my opinion a serious disadvantage. Bilateral septal

FIG. 15. — R. B. Successful bilateral septal transposition.

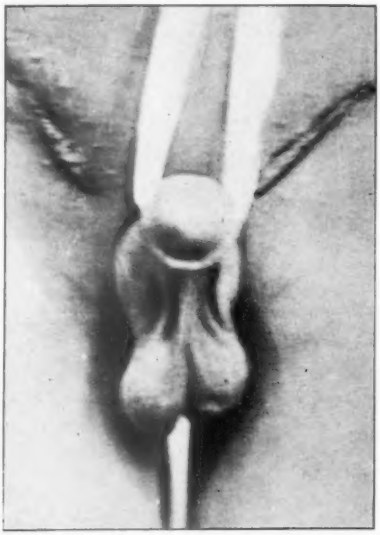


FIG. 16.—J. F. Bilateral septal transposition. The scrotum, owing to each testis being transposed, has a perfectly symmetrical appearance.

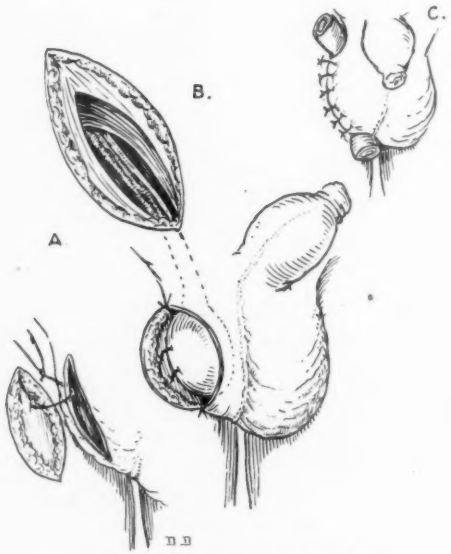


FIG. 17.—The Keetley-Torek operation.

FIG. 18.

FIG. 19.

FIG. 20.

FIGS. 18, 19, and 20.—D. H. Showing the same patient prior to and following the first and second stages of a Keetley-Torek operation. Fig. 19 shows the testis firmly attached to but not deeply buried in the thigh.

transposition is sometimes performed at one operation. This is not advisable unless the testes are extremely mobile as it prevents the bringing up of the septum to meet the testis on either side and may result in excessive tension being placed on the vessels.

The Keetley-Torek operation has proved very successful and gives an excellent cosmetic result. It is difficult to carry out when the testicular vessels are short and has also the disadvantage of being done in two stages. I usually stitch the remains of the gubernaculum or the tunica vaginalis down to the fascia lata and then close the subcutaneous tissues over the testis. This seems to be the most satisfactory way of preventing the testis withdrawing into the scrotum. It think it is also advis able, where possible, to enclose the testis in the tunica vaginalis as the separation from the thigh has in my hands frequently proved more difficult than one would expect. Children suffer no disability when a testis is fixed to the thigh and can always resume

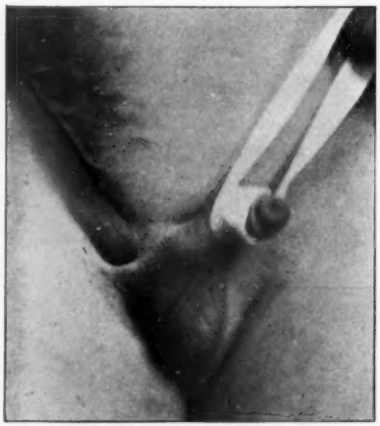


FIG. 21.—D. B. First stage of Keetley-Torek operation completed. The testis is completely hidden in the subcutaneous tissues of the thigh.

FIG. 22.—J. B. Successful Keetley-Torek operation. This patient's left testis descended spontaneously.

their normal life. One of the patients, of whom I have lost track, is still in this condition.

Orchidopexy has been a complete failure on nine occasions. In two instances (Bevan's operation) the testes retracted to their former positions. The testicular vessels were known to have been damaged on three occasions ; in one instance the testis was removed and in the other two there was eventually complete atrophy. In the remaining four cases atrophy of the testes occurred. In one of these a bilateral septal transposition was performed at one operation and it seems probable that too much tension may have been put on the vessels on the atrophic side. The remaining three cases were instances of unilateral incomplete descent in which a normal testis was present on the unaffected side. It therefore seems almost certain that the atrophy must have been due to interference with the blood supply either through trauma or excessive tension.

During the course of these operations two curious anomalies have been observed :—

(1) Descent of the epididymis occurring independently of the testis. This abnormality was found in a boy (J. H. S.) aged 16 years. The left testis was absent from the scrotum and

impalpable. The right testis was normal. At operation, when the inguinal canal was opened, the processus vaginalis was found to extend to the external abdominal ring and a mass palpable at its lower end was considered to be an atrophic testis. During the separation of the neck of the processus vaginalis the vas deferens was observed disappearing into the pelvis and appeared to arise in the nodule at the lower end of the processus vaginalis. No testicular vessels were found and it was feared that they must have been divided. The peritoneal opening was then enlarged and a normal-sized testis was found lying lateral to the internal abdominal ring. The processus vaginalis was completely opened. The vas deferens terminated in the nodule, which represented the epididymis. A small faint line was visible running upwards under the peritoneum from the nodule to the body of the testis and may have represented a drawn-out section of the duct of the epididymis or the efferent ductules. The testis was eventually mobilized and transplanted into the opposite half of the scrotum. The distance between the testis and the epididymis was at least 3 in.

(2) *Bilateral absence of the vas deferens.*—This boy (L. H.), aged 9½ years, was suffering from bilateral incomplete descent of the testes. The left testis was impalpable; the right was felt on one occasion at the external abdominal ring. In June 1938 I performed a right orchidopexy. The testis was lying in the inguinal canal and appeared fairly well developed. No vas or semblance of one was, however, found. The testis was fixed in the scrotum by septal transposition. Last December I operated on the left side, and in view of the previous findings made a very careful dissection. No vas could be found. The testis was retained high up in the inguinal canal. Some descent was obtained after mobilization and a septal transposition seemed possible. In carrying this out the blood-vessels were inadvertently ruptured and the testis therefore became worthless. It was accordingly removed. A transverse section shows testicular tissue, which is normal for the boy's age.

This finding is of interest as ligature of the vas is said to cause atrophy of the spermatogenic tubules and is probably accounted for by the fact that the boy had not reached puberty and the tubules were still in a resting stage.

REFERENCES

BARRINGTON-WARD, L., "The Abdominal Surgery of Children". 1937.
BEVAN, A. D. (1899), *J.A.M.A.*, **33**, 773.
Id. (1903), *ibid.*, **41**, 718.
Id. (1929), *Ann. Surg.*, **90**, 847.
BROWNE, D. (1933), *Lancet* (i), 460.
CURLING, T. B. (1878), "Diseases of the Testis," 4th ed.
DRAKE, C. B. (1934), *J.A.M.A.*, **102**, 759.
DUKES. Quoted in Thomson-Walker, "Genito-Urinary Surgery". 1936.
HUNTER, J., "A Treatise on the Animal Economy", vol. iv. London, 1835.
KEETLEY, C. B. (1894), *Lancet* (i), 1008.
Id. (1905), *ibid.* (ii), 279.
MIMPRISS, T. W. (1938), *ibid.* (ii), 533.
MOORE, C. (1935), *New England J. Med.*, **212**, 422.
MACCOLLUM, D. W. (1935), *Arch. Surg.*, **31**, 290.
MCCREA, E. D'ARCY (1935), *Lancet* (ii), 753.
ODIORNE, W. B., and SIMMONS, C. C. (1904), *Ann. of Surg.*, **40**, 962.
OMBRÉDANNE (1910), *Presse méd.*, **23**, 745.
PACE, J. H., and CABOT, H. (1936), *Surg., Gynec. & Obst.*, **63**, 16.
RAWLING, L. B. (1908), *Practitioner*, **81**, 250.
SOUTHAM, A. H., and COOPER, E. R. A. (1927), *Lancet* (i), 805.
SMITH, R. E. (1937), *Proc. Roy. Soc. Med.*, **30**, 1319, (Sect. Urol. 77).
TOREK, F. (1909), *New York M. J.*, **90**, 948.
Id. (1931), *Ann. Surg.*, **94**, 97.
WANGENSTEEN, O. H. (1935), *ibid.*, **102**, 875.
Id. (1932), *Surg. Gynec. & Obst.*, **54**, 219.
WILLIAMS, PEARSE (1936), *Lancet* (i), 426.

Discussion.—Mr. D'ARCY MCCREA expressed general agreement with Mr. Wilson's conclusions. He preferred, however, to operate at the earliest convenient age, about the fourth year; his reading of Miss Cooper's histological findings on the retained testis was that differences first manifested themselves about that age. He agreed with those who said that organotherapy succeeds

because of increase in size of the testis, and he compared descent at puberty. He doubted whether testes brought down or descending late were ever the equal of a normally descended fellow. He had found the processus vaginalis patent in almost all cases in which the testis was in the inguinal canal or at the internal ring, and inquired what happened to it if delayed descent should occur.

He did not agree that malignant changes occurred in the retained testis of the adult with the frequency to be inferred from Pace and Cabot's histological findings.

Mr. A. SIMPSON-SMITH said too much stress was laid on the age at which to do an orchidopexy, and the more important matter of situation of the testis was shelved. The testis that could not be mobilized through the external ring required immediate operation, irrespective of age, the excess heat and pressure surrounding a testis lying in the abdomen, or inguinal canal, being deleterious even at 2 years of age. Furthermore, if the examining finger found adhesions between the pillars of the external abdominal ring, or more rarely no ring present, then no time should be lost in performing an orchidopexy. Ectopic testes were the third type requiring immediate surgery.

Pregnyl was reserved to encourage very small testes to grow and occasionally to descend. Good results have followed this procedure, but pregnyl is not without danger—redness and swelling of the testes, lengthening of the penis, and in one case an external squint, followed its use. The enlargement of the penis could not be explained as a sign of early puberty, for at normal puberty the organ does not noticeably enlarge.

At the Hospital for Sick Children the Keetley-Torek operation nas been entirely supplanted by a modified Bevan operation. Here a salmon-gut suture attached to the testis is passed through the scrotum and tied to strapping down the inner side of the thigh. The suture can be tightened daily if required, and short vessels are never overstretched, as in the Keetley operation, sometimes to obliteration point. The suture and a long Liston splint on the outer side of the limb to prevent flexion at the hip, remains in situ for fourteen days.

The PRESIDENT spoke in favour of the transseptal method of fixation, which was known to him as the Ombrédanne operation, and he could say from personal experience of a large number of cases that it was an excellent procedure.

One particular advantage of the method was that even a testis which is arrested in the vicinity of the internal abdominal ring can be fixed through the scrotal septum ; this can be accomplished without any important disturbance of the structures of the cord, by simply taking the scrotum up to the testis. As a result of this manipulation there is inevitably obvious tension on the cord, but as the weeks go by this is steadily overcome, so that the testis and scrotum both ultimately assume a normal position. Another interesting point about the Ombrédanne method is that the final result does not give the impression that the transposed testicle lies in the wrong side of the scrotum. Palpation suggests that the implanted organ is lying in its proper scrotal compartment.

Section of Ophthalmology

President—MALCOLM HEPBURN, F.R.C.S.

[*January* 13, 1939]

Foreign Body free in the Globe.—FRANK LAW, F.R.C.S.

A. W., aged 30, gives a vague history of getting a foreign body in the right eye in mid-August 1938, when "some cement blew in". Two weeks later he presented himself at hospital stating that he could see the foreign body in the eye. He can still produce it by suitable posturing, when a small black speck is clearly seen, slowly falling to the bottom of the anterior chamber. It is non-magnetic and, as far as can be ascertained, non-metallic. Is it a piece of uveal pigment? Vision $\frac{6}{6}$.

Persistent Hyaloid Artery in an Aphakic Eye.—G. J. O. BRIDGEMAN, F.R.C.S.

R. U., aged 27.

Left eye aphakic. Persistent hyaloid artery.

The right eye shows no abnormality. The left eye had some form of congenital cataract, and was needled when the patient was 13 years old; the condition then becoming evident. The persistent hyaloid vessel runs forward from the optic disc to a point on the nasal side of the pupil. The eye is amblyopic, vision not being improved beyond hand movements.

Jaw-winking (Marcus Gunn Phenomenon).—STEWART MACKY, M.B., D.O.M.S. and A. RUGG-GUNN, F.R.C.S.

Mr. STEWART MACKY: The patient, W. E., is a boy aged 8 years. There is a movement of the left upper eyelid during the act of chewing; this has been present from birth.

R.V. = $\frac{6}{5}$. L.V. = $\frac{6}{6}$.

Mr. RUGG-GUNN: Jaw-winking is an expressive but not particularly accurate name for this condition; until we know more about its pathogenesis I think that the description, Marcus Gunn phenomenon, is preferable.

The present case is a typical one. His eyes and general health are perfectly normal, except for a unilateral blepharoptosis. The ptosis is not only unilateral but it is incomplete and it is on the left side. A very large proportion of cases agree on these points. Further, the ptosis and the jaw-winking are congenital. Acquired

cases have been described but are rare ; bilateral cases are known ; and some other variations from the common type occur.

The characteristic feature of the phenomenon is that the raising, not the winking, of the affected eyelid is synchronous with and proportionate to the opening of the mouth, and reaches its maximum at the moment that the lower jaw is at its lowest point. The eyelid is usually retracted above the limbus so that the palpebral aperture of the affected eye, which in repose is less than that of its fellow, is now wider. As the mouth closes the eyelid drops. These two movements continue during eating. Passive or active elevation of the eyelid has no effect on the movements of the jaw, nor does passive depression of the jaw retract the eyelid.

The act of mastication has three main components : (1) depression of the lower jaw, mainly by the mylohyoids and digastric muscles ; (2) lateral or grinding movements by alternate action of the two external pterygoid muscles ; (3) outward thrust of the lower jaw, by simultaneous action of both external pterygoids.

Any one of these three groups of movements may produce the jaw-winking syndrome. The nerves involved are the 3rd and the motor division of the 5th.

Ever since the phenomenon was demonstrated in 1883 by Marcus Gunn, attempts have been made to discover some site of anastomosis between the two neuromotor systems. The Ophthalmological Society of the United Kingdom appointed a committee to investigate the problem. The Committee consisted of Gowers, Lang, Mackenzie and Abercrombie, one of whom, Mr. William Lang, only died last year. It has been suggested that it is an example of associated movements. We know, for example, that when the attention is strongly held, staring eyes and an open mouth is a common expression. The fact, however, that the phenomenon is nearly always unilateral seems to negative this explanation.

Topographically, the nuclei of the 3rd and 5th (motor) nerves are not far apart, and some connexion, not so far demonstrable, between them may be surmised. Against this there is the evidence of embryology, which shows that they develop in separate columns. Connexions in the cortex, in the co-ordinating systems, and even in the peripheral nerves have also been proposed, but with little in the way of evidence. It has also been suggested—and this view appears to me to be attractive—that the inter-connexion between the two systems may occur in the posterior longitudinal bundle.

What would happen if a Motais' operation were performed for the ptosis ?

Mr. LEIGHTON DAVIES said, in the case of the jaw-winking movement, that the posterior longitudinal bundle was most likely to be affected. This bundle united all the central nuclei, connecting the cranial nerves and the 5th very intimately, and it seemed to him most likely that some of the fibres might have gone astray and connected too intimately.

Effect of Hypoglosso-facial Anastomosis on Closure of Eye in a Case of Facial Palsy.—A. RUGG-GUNN, F.R.C.S.

T. P., female, aged 26.

R.V. $= \frac{6}{9}$. L.V. $= \frac{6}{18}$.

After a mastoid operation six years ago patient suffered from paralysis of the left side of the face and was unable to close the left eye. The eyelids were sewn together for a year after the operation. She now complains of epiphora, largely due to eversion of the lower punctum. The epiphora is not present while she is lying down. Recently the left hypoglossal nerve has been grafted into the facial, with considerable benefit to the palsy, but now she can close the eye only when she puts out her tongue. The closure of the eye is only complete with full extrusion of the tongue.

Double Congenital Cataract involving the Infantile Nucleus.—A. RUGG-GUNN, F.R.C.S.

H. C. R., male, aged 32. Insurance agent.

R.V. = $\frac{6}{60}$, with glasses $\frac{6}{18}$. L.V. = $\frac{6}{24}$?, with glasses $\frac{6}{12}$.

Ophthalmoscopically the cataract resembles lamellar cataract, but there are no outriders. With the microscope and slit-lamp the infantile nucleus of both lenses is seen to be completely invested by a bright silvery zone, powdery in appearance. Within, the nucleus is clear except that in its centre the fœtal nucleus is well defined and in part faintly opaque. The patient is edentulous.

Discussion.—Dr. HARRISON BUTLER said that he thought the cataract was a very delicate one and one which formed early in the life of the lens. In two cases of his own he had been able to find out the cause. One had an abscess of the brain and was seriously ill for a whole year, and was operated on and recovered. The age seemed to coincide absolutely with the position of the cataract in the lens. He had a second case of similar nature. The case now shown by Mr. Rugg-Gunn was, he thought, too early to be due to anything which occurred after birth, and it was probable that some intra-uterine condition had caused it.

Mr. C. B. GOULDEN said that the condition was pictured in Vogt's Atlas. It was congenital in nature, and named cataracta centralis pulverulenta.

Senile Macular Exudative Retinitis.—A. RUGG-GUNN, F.R.C.S.

B. P., female, aged 74.

R.V. < $\frac{6}{60}$. L.V. < $\frac{6}{60}$.

First seen a year ago, when she complained that " everything had looked crooked " for a month. At the right macula there was a deeply pigmented mass which seemed to project forwards and was situated rather low in the macular region. The area was roughly oval and about two disc-breadths in diameter. The pigment was dense black in parts ; in others of a dirty wash-leather colour. External to it was a somewhat elongated recent hæmorrhage. Small hæmorrhages were present chiefly in the lower part of the fundus. There was a lesion also in the left macula. This was not raised and consisted of fine granular pigment, rather curiously disposed in radiating lines. It has altered very little during the past year, but the linear arrangement is now less obvious. The retinal arteries were not sclerosed.

The patient was admitted and an attempt made to transilluminate the mass in the right eye through a conjunctival incision. This procedure was successful in that it showed the pigment to be superficial, i.e. confined to the summit of the growth, which itself appeared to be cystic and transmitted light.

Now after a year, the condition at the right macula is very different. It shows a raised tumour, more than three disc-breadths in diameter with clear-cut edges, and raised at its summit at least 4 diopters. The pigment has entirely disappeared, and the growth is yellowish-white in colour but has an indefinite grey area on the summit. There is no detachment of the retina, but on focusing the margin of the growth on the temporal side fine parallel striations can be seen, probably lines of stress. There are no fresh hæmorrhages, but there is an extensive area of superficial choroiditis, comparable to the macular condition in the left eye, in the lower and external part of the fundus.

The blood-pressure is 190/100 and there is no albuminuria.

This is not an unusual case, but it is interesting in that all the signs of hæmorrhages and so forth have completely disappeared with the maturation of the tumour. As I

have stated the pigment has now entirely disappeared, but at one time it was densely black and pigmented all round, and floating more or less on the anterior surface. There is an area of choroiditis with small granular pigment down below, very similar to the earliest aspect of the condition which is present in the left macula.

The PRESIDENT suggested that this condition frequently arose from obstruction in some of the choroidal vessels.

Acute Uveitis: Second Eye affected 16 Years after the First.—A. RUGG-GUNN, F.R.C.S.

J. C. L., female, aged 37.

First seen by me in August 1922, when she gave a history of blurred vision with distortion of objects lasting three months.

R.V. $= \frac{6}{6}$. L.V. $= \frac{6}{6\,0}$.

Left K.P. present; hazy media and slight circumcorneal injection. Fundus seen very indistinctly but no lesion noticeable. A history of severe tonsillitis eighteen months before. The condition rapidly got worse. The ciliary injection increased and the cornea became almost obscured by K.P., some of the deposits being of " mutton-fat " appearance and massive. After some five weeks the eye began slowly to improve. A physician examined the patient, who was then aged 20, and pronounced her general condition good, with the exception of the tonsils. The latter observation was confirmed by a laryngologist, and subsequently the tonsils were removed. Evidence of tuberculosis was sought for unsuccessfully. During this period injections of Witte's peptone were given. When the cornea cleared widespread retino-choroiditis was observed, involving the whole fundus, and the left eye has remained practically blind.

Sixteen years later, i.e. in the beginning of last May, the right eye suddenly developed a central scotoma and a small indistinctly defined lesion was present at and above the macula. The patient gave a history of having had the lingual tonsil removed and the antra washed out two years ago.

Various investigations were now undertaken, including X-ray examination of the alimentary canal, teeth, and sinuses, the Wassermann reaction, blood-count and gynæcological examination, and everything was negative, except that the sedimentation-rate was slightly increased. X-rays of the chest were negative and so was the Mantoux reaction.

The patient was given a series of intramuscular injections of milk; short-wave applied locally; and various other forms of treatment including sulphanilamide, but the condition continued to get worse and appeared to be developing into the same state as the left eye, although there was less K.P. and in other ways also it was less acute. Finally, not only the central part but practically the whole fundus was affected.

At this stage, although the sinuses had been X-rayed more than once, I decided to have stereoscopic X-ray plates taken, with the result that sinusitis of the left sphenoidal sinus was disclosed. The sinus was drained by Mr. Glennie, and from that time the patient began to improve.

I have shown the case because the fact of each eye being affected, after an interval of sixteen years, presumably by toxins from a septic focus, suggests some special selectivity of the infecting organism for uveal tissue or some sensitivity of the uveal tissue for the particular toxin; also to illustrate the value of stereoscopic X-rays in the examination of the cranial sinuses.

? Macular Cyst.—W. HARRIS, M.D. (for Mr. RUGG-GUNN).

P. S., male, aged 8 years.

R.V. = less than $\frac{6}{60}$. L.V. = $\frac{6}{6}$.

In July 1938 a prominent rounded mass was visible in the right macular region with a circumscribed area of œdema. Small vessels appeared to be running over the edge of the mass around the whole of its circumference. In October the mass appeared to have slightly increased in size, and a high light reflex was present. The vessels and the œdema were more marked. A small hæmorrhage had occurred on the temporal side of the mass. Small veins appeared at the disc margin, and seemed to be varicose in nature. At the present time (January 1939) the hæmorrhage has resolved and the mass appears pale. A few specks of pigment are seen in the retina overlying the lower part of the cyst. Opinions are agreed that the mass is not neoplastic, but there is disagreement as to its being cystic or inflammatory in nature.

Eales' Disease.—W. HARRIS, M.D. (for Mr. RUGG-GUNN).

H. K., male, aged 36.

This man was seen on November 23, 1938, for "cloudy vision" in the left eye which had persisted for two weeks. He had been treated at the Royal Westminster Ophthalmic Hospital eleven years ago for hæmorrhage in the same eye. His vision was: R.V. $\frac{6}{9}$, L.V. $\frac{6}{12}$. The right fundus showed vitreous "floaters" and macular œdema; the right fundus also showed obliteration of the distal end of the superior temporal branch of the retinal vein. An anastomosis had occurred in this region which appeared angiomatous in nature. It was suggested that the condition might bear some relation to Von Hippel's disease. The left showed vitreous hæmorrhage, retinitis proliferans, and choroidal scars temporally. In December the left vision became worse, dropping to $\frac{6}{60}$ from $\frac{6}{12}$. The Mantoux reaction was weakly positive. In the right fundus also the vitreous "floaters" were more pronounced.

An Operative Technique for Retinal Detachment

By EDWARD C. ZORAB, M.B., D.O.M.S.

A LITTLE over ten years ago Gonin first described his operation for cautery puncture in cases of retinal detachment, since when a host of various methods have been described. All of them have produced some good results, especially in the hands of their originators. The use of diathermy has become increasingly popular in spite of the comparatively expensive apparatus involved, partly because the results have been more satisfactory, and partly also I think because no great technical skill is necessary as was the case with Guist's method or with simple multiple trephining. Anyone can do a diathermy operation after a fashion, but unless a great deal of trouble is taken before, during, and after the operation, the results will be no more successful than the old method of putting the patient to bed for a few weeks. I have no original method to offer; I merely intend to outline a fairly simple method which is giving reasonably good results.

One of the essentials for success is the finding of a retinal hole, a tear, or a disinsertion. It is very probable that one of these exists in every case except for the solid, the cystic, and the inflammatory types of detachment. In the majority of cases the

finding of the hole presents no great difficulty, though it must be borne in mind that more than one such lesion may coexist. For this reason it is advisable that a sketch of the fundus, in which all the vessels are included, be made in every case. Furthermore, the sketch should be made by the surgeon who is to perform the operation. This ensures not only that every part of the fundus has been observed, but that the operator is thoroughly familiar with the conditions obtaining in the fundus. If no hole can be found by ordinary observation it is sometimes helpful to anæsthetize the eye and observe the periphery of the fundus while an assistant presses in the sclera with a glass rod over an area corresponding to the ora serrata. An ophthalmoscope of the Lister-Morton type with a 12-volt bulb working off the mains is also an advantage. The operation is based on the method of Professor Weve of Utrecht. The only special instruments required are indian ink, Amsler marker, Arruga's retractor, Larsson type ball applicator, Weve points, also unipolar spark-gap diathermy machine, giving readings up to 300 ma. A single lead goes from the machine to the applicator, the usual indifferent electrode fixed to the patient's arm being unnecessary.

Pantocaine seems to be the most satisfactory anæsthetic augmented by an injection of about 2 c.c. of novocain into Tenon's capsule in the region to be approached. Provided only one or two drops of $\frac{1}{2}\%$ pantocaine are used the cornea should remain clear throughout the operation. The conjunctiva and Tenon's capsule are opened with a good wide incision, and one or more muscles divided if necessary. It may be sufficient only to make a small snick with scissors in the lateral part of the tendon at its insertion, thus avoiding the necessity of putting in sutures afterwards. The sclera is thoroughly cleaned and hæmostasis secured in the ordinary way. Arruga's retractor is then inserted and the eye rotated, voluntarily if possible or assisted by forceps, in the direction of the hole. With the theatre darkened the operator locates the hole with the ophthalmoscope, and while still observing the hole the light is focused down to the smallest possible point. The assistant will then see a small circle of light shining through the sclera which he marks with indian ink. A subsequent check is made to ensure that the ink mark is in the right place. With a large tear or a disinsertion it is advisable to outline the limits of the lesion with ink marks. An area of surface diathermy is then made with the ball applicator using a current of about 150 ma. Care must be taken to avoid excessive charring of the sclera. The current necessary can best be controlled by the amount of reaction observed ophthalmoscopically. The surface diathermy should provide a bed of choroidal coagulation on which the torn retina will fall back leaving a margin the size of which should depend on the condition of the surrounding retina. After the surface diathermy has been made the intra-ocular pressure will be found to be considerably raised, and the cornea may have become hazy. A number of diathermy punctures are next made outlining the hole, using a current of about 100 ma., and a point of sufficient length almost to touch the retina. The point should be applied to the globe with the current switched on, when it will perforate as easily as the actual cautery. The punctures, which should all be made within the area of surface reaction, will produce a round white mark in the retina which can easily be seen ophthalmoscopically. Subretinal fluid is aspirated after each puncture with a pipette or the top of a Chalk's bottle, and the site of the puncture checked by observation. After the first puncture the cornea will again become clear owing to the lowering of the intra-ocular pressure. These punctures followed by aspiration should be repeated until the retina can be seen to be lying almost flat on the bed of coagulated choroid. The incision is then closed, the eye atropinized, and both eyes bandaged.

It has always been advocated that the patient's head be so adjusted after operation that the scleral punctures are the most dependent part of the eye. I do not think that this is necessarily the most advantageous position. The punctures very rapidly

close up—probably within a few hours—and the residual subretinal fluid, of which there is always some, gravitates down towards the punctures and therefore towards the hole or tear. Not being able to escape it lifts the torn retina off the bed of coagulation, thus defeating the object of the operation. I believe that the patient's head should be so arranged that the residual fluid will neither interfere with the operated area nor tend to detach any further area of retina. Provided that the hole has been closed this fluid will eventually be absorbed, and while absorption is taking place the fluid should be located by gravity in the situation where it will do least harm. In the case of a small localized detachment practically all the fluid is evacuated at the time of the operation, and the post-operative position is not of very great importance.

With regard to the marking of the hole on the sclera an error enters into the method in the case where the hole is located on the summit of a balloon, unless this be situated at the posterior pole of the eye. It has been shown mathematically and experimentally that a shift forward of the retina of 1 mm. corresponds to an alteration of 3 diopters in the refraction of the eye. Suppose that a hole can be sharply focused on the summit of a balloon with a $-1{\cdot}0$ lens in the ophthalmoscope, and the disc with a $-10{\cdot}0$ lens. The difference of 9 diopters means that the retina is approximately 3 mm. away from its bed in the region of the hole. When the ink mark is made on the sclera it must therefore be made at a small distance from the patch of light towards the limbus. This distance is just over 1 mm. for every 3 mm. of separation.

It is too early to give statistics of this method. However, the percentage of patients leaving hospital with their detachments replaced has been definitely increased. A full analysis of the results will be published from Moorfields at a later date. Although the results of detachment operations in this country are improving they are still well behind the leading countries. I think the chief reason for this is the time factor. In most of our hospitals both the Honorary and House Staff are fully occupied, consequently insufficient time is available for individual cases. Until a solution is found for this state of affairs our results will be unable to compete with those of the leaders.

Mr. CHARLES GOULDEN said: When Gonin first brought forward his method of treating detachment of the retina he made the classic remark that the treatment depended upon "the permanent stopping up of the passage by which the liquid of the vitreous humour passes into the subretinal space". This he proposed to do by means of a Pacquelin cautery introduced in such a way that the edges of the hole in the retina were actually seared and then fell upon a patch of choroiditis prepared for it. This needed very careful preliminary investigation and plotting so that the area of the sclera perforated should coincide with the retinal hole. The results of the operation were surprisingly good, but only small holes in the retina could be successfully dealt with. In any event Gonin himself picked his cases carefully so that patients with at that time a hopelessly large tear, or with a very old detachment, should not be operated upon unnecessarily. The next stage in the development of the treatment of detached retina was the chemical method associated with the name of Guist, followed shortly after by the method of surface diathermy introduced by Larssen. By these means much larger holes could be dealt with and there followed a much less precise and more careless method of operation. Less care was taken in localizing the hole as compared with the method introduced by Gonin and what I may term the operative method of the "long shot" was introduced in which liberal applications of either caustic or diathermy were applied to some particular quadrant of the sclera in a somewhat erratic way. The method now applied was not that by means of which the hole in the retina itself was attacked, but a "barrage" as it was called, was put up by means of which it was hoped that the hole in the retina might be isolated. The results were possibly better than those achieved by Gonin's method especially when we remember that disinsertions could now be treated, a form of retinal defect that gives an especially good prognosis after operation.

We were still in need of a method of localization, which should be precise and simple. This is

now available, and if applied and combined with an ophthalmoscopic control of the results within the eye of diathermy applied to the sclera, much greater success in treatment has followed. As Mr. Zorab has mentioned, the method of localization is that of transillumination. Incidentally, this method was proposed to me several years ago by Mr. Fincham, but I had not the intelligence to appreciate his suggestion ; but I would mention that at that time Arruga's spoon had not yet been devised, nor the importance of indirect ophthalmoscopy appreciated.

Now that precise operating is possible, we have reverted to Gonin's original plan of attacking the hole in the retina itself. By carefully plotting the area of the hole in the retina on the sclera with indian ink we can now apply the diathermy terminal to the sclera so as to cause coagulation of the edges of the hole itself as well as to form a bed of choroiditis on to which the retinal hole may fall precisely.

Professor Weve, to whom this precision is due, combines surface diathermy with puncture diathermy so that the edges of the hole of the retina are nailed down by a puncturing needle introduced so as to touch the edges of the hole at several places. Successes are obtained by this technique which are far superior to those obtained by any other, and in early cases successes comparable with those seen in cataract extraction are obtainable.

By the method of barrage, especially when applied without ophthalmoscopic control, 40–50% of cases of detachment may be cured, but by the method adopted by Professor Weve, all cases of disinsertion should be cured, and in skilful hands 85% of all cases cured even when all cases that come for treatment are undertaken.

I would like to mention certain essentials that are necessary for success.

There must be a most careful investigation of the case by the surgeon himself which cannot be delegated to others if the best results are to be obtained. This investigation consists, among other things, of

(1) A most careful examination by ophthalmoscopy for which is essential

(*a*) A maximum dilatation of the pupil.

(*b*) The greatest possible intensity of light. For this purpose a 500 candle power lamp in a suitable casing is needed.

(*c*) Indirect ophthalmoscopy with a mirror of 25 cm. length, behind the sight hole of which is a +4·00 D sphere and an illuminating lens of +20 D of 3·4 cm. diameter.

(2) A sketch made by the operating surgeon of the whole eye, not only of the area in which the hole is found.

This is the method followed by those who have done most to develop the technique, Weve, Amsler, Arruga, and Gonin. Vogt certainly uses the indirect method of ophthalmoscopy, but I am not sure whether he personally makes his own fundus sketches.

Another most important requirement is team work. There must be a surgeon and his assistant who understand one another perfectly. There must be someone in charge of the instruments who is alert all the time and who knows all the stages of the operation. There must be an assistant to hold the large lamp and one other in charge of the diathermy apparatus, and who is also in charge of the general illumination of the theatre, so as to extinguish and restore the light as needed. Personally, I think these detachment operations can only be done successfully in large centres where many cases come for treatment, and owing to the amount of time needed both for the preliminary investigation and for the operation itself it seems to me that something in the form of detachment clinics must be set up in various large centres comparable to fracture clinics. It is not yet apparently appreciated that after operations for cataract, glaucoma, and squint, operations for retinal detachment are the commonest, which is remarkable when it is remembered that the first modern operation for detachment of the retina done in this country was in January 1930.

Prevention of Industrial Eye Injuries

By J. Minton, F.R.C.S.

Eye injuries in industry are increasing every year. This increase is the result of the expansion of the engineering and metal trades. At the Royal Eye Hospital, London, 7,000 industrial eye injuries are treated every year, many of which are of a very serious nature. In the course of my investigations I visited many factories, both in London and the provinces. I found that the medical officers attached to these factories were treating more injuries to the eyes than to any other part of the body. One large armament establishment in London employing several thousands of workmen deals with 15 to 20 eye injuries a day. A similar occurrence was observed in the Great War, when a large increase of industrial eye injuries was reported by the Ministry of Munitions dealing with Industrial Health and Efficiency. This report was published in 1918.

The greatest number of eye injuries keep the workmen from employment for a period of from half a day to one or two days. Such injuries are therefore followed by a great loss of working hours and loss of wages.

Severe industrial eye injuries (intra-ocular foreign bodies, perforating eye injuries, hypopyon ulcer, &c.) often result in the loss of an eye and more rarely lead to total blindness. An analysis of reports on the blind from various countries published by the International Association for the Prevention of Blindness in 1937, shows that 5% of the blind have lost their sight as a result of accidents in industry. Industrial eye injuries more commonly lead to the loss of one eye only and, according to Trousseau (France), accidents in industry are responsible for 20% of uni-ocular blindness.

The largest number of eye injuries occurs in the metal and engineering trade, but wood-work, working coal-mines, chemical industries, quarrying, stone-cutting, masonry and concrete work, have a high incidence of injuries.

Eye injuries in industry belong to the preventable class of accidents. The Travellers Insurance Company of America has come to the conclusion that 88% of such accidents could be avoided by proper supervision and administration. The widespread use of safety devices by individual workmen and the guarding of machinery will eventually lead to a great diminution of eye injuries.

The factory legislation of this country, until the 1937 Factories Act, had no general section for eye protection. The provision of goggles, screens, and masks, &c., was left to the discretion of the individual employer. Many progressive firms desiring to obtain a maximum efficiency from their employees and to prevent loss of working hours have spent much effort in providing the workmen with efficient and suitable safety devices and in educating the workmen in their use. The results achieved in these factories is praiseworthy. The Great Western Railway, Imperial Chemical Industries, Kodak Ltd., and many others report a great diminution of eye injuries as a result of their efforts.

The conditions of intensive production during the Great War gave an impetus to the study of working environment and accident prevention. Voluntary bodies such as the National Safety First Association, founded in 1916, and the Industrial Welfare Society, founded in 1918, have carried out much educational and propaganda work.

The Factories Act of 1937 began a new era in the history of eye protection, which for the first time has received statutory mention. Section 49 of the Act reads as follows :—

" In the case of any such process as may be specified by regulations of the Secretary of State, being a process which involves a special risk of injury to the eyes from particles or fragments thrown off in the course of the process, suitable goggles or effective screens shall, in accordance with any directions given by the regulations, be provided to protect the eyes of the persons employed in the process."

Although until the 1937 Act there was no general section dealing with eye protection there were some requirements such as :

(1) Under the 1891 and 1895 Acts—

(*a*) Special rules for the bottling of aerated waters. These require the provision of face guards, masks or veils of wire gauze for wirers, sighters, and labellers.

(2) Under the 1901 Act—

(*a*) Regulations for the use of locomotives and wagons on lines and sidings provided that all glass tubes of water gauges on locomotives or stationary boilers used for the movement of wagons shall be adequately protected by covering guard.

(*b*) Aerated Water Regulations. These replace the special rules 1 (*a*) above and impose a similar requirement.

(*c*) Chemicals Works Regulations where acids or corrosive liquids are used. Goggles were required to be provided and eye-wash bottles containing distilled water.

(*d*) Woodworking Machinery Regulations. The means of artificial lighting for every woodworking machine must be so placed or shaded as to prevent direct rays of light from impinging on the eyes of the operator while he is operating the machine.

(*e*) Horizontal Milling Machine Regulations. A similar requirement to (*d*) above.

(*f*) Shuttles guards were required for looms in textile factories under various trade agreements.

(3) Under the Police, Factories (Miscellaneous Provisions) Act 1916, first-aid cabinets containing eye-drops were required in every factory.

In the early years of the century the Factory Department began to give close attention to industrial lighting. In 1913 a Departmental Committee on Lighting was appointed and issued reports in 1915, 1921, and 1922. A fourth report was issued recently by the reconstituted committee bringing their recommendations up to date. Research into lighting requirements has been carried out by the Industrial Health Research Board and the Illumination Research Committee of the Department of Scientific and Industrial Research.

The Factories Act of 1937 constitutes a landmark in industrial ophthalmology of which the ophthalmic profession should be made conscious. The Secretary of State acting under section 49 of the Factories Act, issued on July 5, 1938, regulations which came into force on August 1, 1938. The regulations make it compulsory for the employer to provide protection for the eyes (goggles, screens, masks, &c.) in the occupations set out below.

Dry grinding of metals or articles of metal applied by hand to a revolving wheel or disc driven by mechanical power.

Turning (external or internal) of non-ferrous metals, or of cast iron, or of articles of such metal or such iron, where the work is done dry, other than precision turning where the use of goggles or a screen would seriously interfere with the work, or turning by means of hand tools.

Welding or cutting of metals by means of an electrical, oxy-acetylene, or similar process.

The following processes when carried out by means of hand tools or other portable tools :—

Fettling of metal castings involving the removal of metal.
Cutting out or cutting off (not including drilling or punching back) of cold rivets or bolts from boilers or other plant, or from ships.
Chipping or scaling of boilers or ships' plates.
Breaking or dressing of stone, concrete, or slag.

These far-reaching regulations are bound to have a great effect on the diminution of industrial eye injuries, but they can only achieve their purpose with the co-operation of the medical profession at large and ophthalmic surgeons in particular. The working-class population must be educated in the use of the correct protective devices and the employers must be advised on the suitable type of protection they must supply to their employees. The workmen, as a result of years of prejudice, are ashamed and resentful of wearing masks or goggles, &c. The employers have in the past supplied uncomfortable and unsuitable goggles with which the employees have been unable to turn out the maximum output demanded of them. These protective devices were therefore discarded. The compulsory wearing of goggles following the recent Home Office regulations can only become successful if the research work on the production of such protective appliances keeps pace with the factory requirements. The eye hospitals in this country and the ophthalmologists practising in industrial districts should take an active interest in the educational aspect of this problem.

Following my investigations of industrial eye injuries in 1936 the Royal Eye Hospital, has taken an active part in the campaign against eye injuries in industry. A comprehensive collection of protective appliances is exhibited in the hospital waiting rooms. Posters are displayed in prominent positions all over the hospital urging the workmen to protect their eyes when at work. A record is kept of all industrial eye injuries and the names of the firms where they took place. At regular intervals letters are sent to firms in the neighbourhood from which 25 or more eye injuries have come. The employers are advised of the number of eye injuries at their works and are asked to visit the hospital. They are then shown suitable protective appliances. In most instances the response from the firms is cordial and the advice given them is accepted with gratitude. It is surprising how little is known about the recent developments in the production of goggles. Old and inefficient types are still used in many factories. It is therefore not to be wondered at that the workmen refuse to wear them. There are now a number of goggles on the market which are almost ideal in their design. They are light, do not impede vision, and can be used with an anti-dimming compound which prevents condensation of moisture on the lenses. In oxy-acetylene and electric welding and for furnace workers goggles should be fitted with glass designed to cut out infra-red and ultra-violet rays. The British Standards Institution has laid down specifications for protective glass suitable for welding. In spite of this, cobalt blue glass is still used although in such operations it has been found most inefficient for its purpose. All these points are explained to the employers when they require advice on suitable eye protection.

A united and co-ordinated effort on the part of the eye hospitals and British ophthalmologists is necessary to educate the employer and employees in eye protection. The establishment of exhibitions of protective appliances in all eye hospitals and the appointment to such hospitals of medical officers acquainted with industrial problems, who should act as advisers to the employers and workmen, would, in my opinion, be a great advance in the campaign against eye injuries in industry. The formation by the British Council of Ophthalmologists, or by any other body of ophthalmologists, of a committee working in co-operation with industry and the Home Office authorities in the improving of protective devices and evolving efficient eye protection

is a question of urgent importance. Records should be kept by eye hospitals of all industrial eye injuries. They would reveal the industrial processes which are responsible for a large number of these accidents, and which are not covered by compulsory legislation. The Secretary of State has the power under Section 49 of the Factories Act to extend the regulations for eye protection to any process which involves a risk of injury to the eyes. Information could then be supplied from hospital records of industrial eye injuries to an appointed body of ophthalmologists who would then advise the Secretary of State on other processes requiring extension of factory legislation.

[At the conclusion of this paper a cinematograph film demonstrating methods of protecting the eyes of industrial workers was projected. Mr. Minton also exhibited specimens of goggles, shields, and other protective wear.]

Discussion.—Mr. JOHN MARSHALL asked what was the life of a goggle or protective shield such as had been shown when it was worn by, say, a worker on a grinding machine. He thought it must be relatively short. A good transparent piece of glass was likely to become obscured by the settlement of fine particles.

Mr. J. MINTON (in reply), said that the life of the goggle depended on the process at which it was used. In chipping and hammering, where large particles flew towards the goggle, there was no deposit on the glass. In the case of grinding or in oxy-acetylene welding the deposit of particles did tend to obstruct the vision, but the glass, whether non-splinterable or ordinary glass, could be taken out and replaced very easily. Cellulose acetate goggles were very cheap and could easily be replaced. It was up to the workman, when he found that the efficiency of his goggle had deteriorated, to ask for replacement.

He wished to add that anyone who was interested in the film could obtain the loan of a copy by applying to the Industrial Welfare Society or the National Safety First Association, in the libraries of which institutions copies had been deposited, or to the Royal Eye Hospital. The film was doing some very good propaganda work.

JOINT DISCUSSION No. 3

Sections of Surgery, Medicine and Anæsthetics

Chairman—C. H. S. Frankau, C.B.E., M.S.

(President of the Section of Surgery)

[*February* 1, 1939]

DISCUSSION ON SURGERY IN DIABETIC PATIENTS

Mr. J. B. Hunter (Surgery): The treatment of diabetes now allows the complete control of the diabetic condition, so that more cases are suitable for surgery than in the pre-Banting era; and, because of the increased length of life, a larger number of diabetic patients come to surgeons with conditions incidental to the disease. The figures at King's College Hospital show that in the years 1919–23 the total number of diabetics admitted to medical and surgical beds was 68, whereas, in 1933–37 the number admitted was 730. In the first period there were two cases of gangrene and in the second period 39 cases.

There are two types of cases: first a group in which surgery is considered necessary in a patient suffering from diabetes, and second one in which surgery is necessary on account of some complication of the diabetic condition. The latter group can be subdivided into cases in which sepsis is the predominant feature and those in which the disease is being aggravated by factors which affect the metabolism.

When surgery has to be undertaken in a diabetic patient, the risk of operation has to be assessed by the general condition and the reaction to diabetic treatment, and one is naturally guided by the physician in charge of the case. It may be stated broadly there is no greater risk in operating on a properly prepared diabetic patient than on a non-diabetic one; indeed there may be less risk because there is an adequate period of rest and pre-operative treatment, which is not always accorded to the non-diabetic. The same care is, of course, even more essential during the forty-eight hours following operation, and it cannot be stressed too strongly that during this period the closest co-operation is necessary with the physician.

As is well known, two factors play a large part in upsetting the metabolism in these cases, the anæsthetic and the trauma. Severe trauma, especially where there is laceration or cutting of soft tissues, produces in the normal individual a transient rise in the blood-sugar, which is of little importance, but in the diabetic is of greater significance, and in such an operation as radical mastectomy may cause grave post-operative disturbance if the metabolic after-treatment is not adequately supervised. In abdominal surgery severe and prolonged vomiting may occur, and again after-care is of the greatest importance.

I now come to the second group, where surgery is necessitated by some complication of the diabetic state or where the disease is being aggravated by other ductless glands such as the pituitary or thyroid. Pituitary cases are few, but diabetes aggravated by thyroid disease is, however, not uncommon, and does concern the surgeon. In 154 thyrotoxic cases of mine at King's there were eight diabetic cases (about 6%).

In thyrotoxicosis, the diabetic state may be considerably augmented ; the metabolic rate being increased, the patients tend to waste more rapidly when the pancreas is also at fault. The alleviation of the thyrotoxicosis produces a marked improvement in the patient's condition although it does not cure the diabetes, the blood-sugar drops rapidly and the gain in weight averages about 2 st. The administration of Lugol's iodine after operation is of importance as this seems to help the diabetic over a difficult period. Owing to the admirable management by the diabetic department at King's, I have no undue anxiety about the diabetic thyroid.

There remains that very large group of cases in which the diabetic condition is aggravated by sepsis. Most of the obvious septic lesions affect the extremities. Diabetics are extremely liable to infective lesions of the feet, produced by conditions which in the ordinary person would pass unnoticed and would heal unattended. Such conditions as cracks in callosities, too-close paring of corns, and the minor traumas associated with the cutting of nails, are all liable to produce some degree of cellulitis, either superficial or deep. The deeper form seems to be a penetrative type, and we are all familiar with the patient who comes for consultation with a small sinus with little or no reaction around it, which on further investigation leads down, most commonly, to one of the phalangeal or metacarpophalangeal joints. On probing such a sinus, bare bone can frequently be detected. A radiograph reveals complete destruction of the joint with no obvious sequestration to be seen. The sequestra are present, however, and are formed from the cartilage of the head and base of the affected bones. This characteristic lesion is due no doubt to the poor blood supply of the cartilage, which makes it more vulnerable in these diabetic arteriosclerotic patients.

A general examination of the arterial state should be made, first in relation to pulsation in the dorsalis pedis and posterior tibial arteries, an examination that may be very difficult in a fat diabetic with œdema of the foot. The popliteal artery should be examined for pulsation, and considerable help as to the degree of vascular disease may be obtained by examining the radial and brachial arteries. Cases often present themselves in a worse state with spreading cellulitis in the foot, either locally round the original lesion, or with the whole foot involved and a spreading œdema above the ankle. There is, however, one striking fact, the diabetic patient appears to suffer much less pain from such lesions than the non-diabetic. This is a point of considerable importance in treatment, it can be taken advantage of to remove small sequestra from a sinus without an anæsthetic and to dress the wound ; but it should make the surgeon very cautious in the application of strong antiseptics and treatment by radiant heat.

General treatment should be similar to that given in non-diabetic cases with certain modifications, the diabetic state should be ascertained, and put under control. But if the septic condition calls for it, incisions should be made and the area drained at once and the diabetes dealt with afterwards. Where the cellulitic area has to be opened and sequestra removed, the after-care of the wound is important. These cases should be treated by packing them with sterilized boracic powder which is renewed every day. This antiseptic is not powerful enough to damage tissues which have a poor blood supply ; but goes on acting until the next application, and has the further advantage of preventing the part from becoming sodden. After a few days, as the wound begins to heal, a small quantity of insulin is introduced into its depth, once or twice a day. The value of local treatment of such wounds with

insulin is, I know, a debatable one. *In vitro*, insulin mixed with pus or serum is made inactive, and it has been stated that local injection is, therefore, of no value. I do not hold this view. In one case treated by this method, the diabetic state was so improved that it required no insulin ; when, however, the sinus closed and the local insulin treatment was discontinued, sugar again appeared in the urine. In another case, my house surgeon was called to the ward because the patient was suffering from hypoglycæmia after the local insulin treatment. I am aware that there may be fallacies in this argument, but clinical medicine has before this shown that what happens *in vitro* does not necessarily happen *in vivo* ; it is possible that the presence of the slightly acid boracic may determine the fact that the insulin is not destroyed.

At the same time, whether the patients have pulsation at the ankle or not, they are treated with a pulsator. The one I find most convenient is that devised by Dr. Wilson. It can be employed in the ward and several patients can be treated in a day. They have two hours' treatment twice a day, the cycle taking three and a half minutes. In some cases where a chronic sinus is present the removal of the sequestra can be undertaken during the daily dressings ; boracic powder, insulin, and the pulsator being used as before.

The majority of these patients with septic lesions are in the arteriosclerotic period of life, the vascular disease undoubtedly being aggravated by the diabetic state. At any time, therefore, the septic lesion of the foot may pass from sepsis into gangrene and may do so during the first few days of treatment. This may be the result of the increased tension of the part, of surgical incision, or of the application of heat. The last is the most important, as the diabetic foot is apparently more insensitive than normal and a degree of heat sufficient to blister may not be noticed. The extent of the gangrene must determine the line of treatment. If accompanied with a severe degree of cellulitis, amputation is called for at a high level ; if there is little cellulitis local amputation may be sufficient. In either event, except on rare occasions, the patient should be treated for a period in bed with dry dressings. If improvement follows, such as reduction of œdema, it is advisable to wait until the maximum has taken place before amputating, but it must be stressed that the area should be carefully watched as the condition can become rapidly worse in a few hours, and may demand urgent surgery. The amputation of toes for osteomyelitis and gangrene can and should be undertaken in suitable cases. The operation area does not usually break down, and if it does, the patient has had a chance of the minor procedure. In amputations other than those above the knee, it is inadvisable to use a tourniquet, as it may cause thrombosis of the smaller vessels in the neighbourhood of the wound.

The site of amputation will be determined by the extent of the gangrene, the vascular condition in the limb, and the general condition of the patient. If the arterial condition is good and the area of gangrene small in extent, local amputation can be undertaken ; if, however, the arterial condition is poor and the cellulitis is of a spreading character, amputation has to be undertaken above the knee. In old patients, diabetes is usually of short duration, and when they develop septic lesions of the feet gangrene often follows. Delay in operating may be fatal, and the site of such amputations should always be above the knee.

Another septic lesion that calls for special mention in the diabetic is carbuncle. This is most commonly seen on neck or back, and tends to reach a huge size and have a rapidly detrimental effect on the patient. Where the carbuncle is seen early and is small, treatment by magnesium sulphate paste should be instituted, as in the ordinary patient ; where, however, the carbuncle is large, or is spreading in spite of treatment, it should be radically dealt with by turning up four flaps of skin and cutting out the dead tissue. The diabetic patient does not seem to be able to tolerate the presence of a slough and its separation.

In a surgical emergency time should not be wasted in treating the diabetes, apart from steps to tide the patients over the operation. These patients are liable to

abdominal cramps, which may simulate an acute abdomen. This may cause some difficulty in diagnosis as their pain sensation is altered, and for lack of signs and symptoms such a disease as acute appendicitis may well be overlooked.

In conclusion, the importance of the surgical aspect of diabetes should be stressed. It has been stated that every other diabetic is a surgical case before it dies. The physicians have done their part, the medical mortality, according to American figures, being reduced to about 2%; but the surgical mortality is about 12%. As this 12% is due mainly to septicæmia, new lines of treatment may further reduce the surgical mortality rate.

Dr. H. P. Himsworth (Medicine): It is a tradition in surgery that diabetic patients support surgical treatment badly. Nowadays this view is no longer justifiable; in the majority of operations on diabetic subjects, provided the diabetes is properly controlled, the surgeon may completely disregard the fact of the patient having diabetes and may proceed to attack the local lesion with the same technique and with as much confidence in the ultimate result as in an ordinary case. In all operations on diabetic patients, however, the physician in charge of the case must decide whether or not the state of the diabetes will permit the application of unrestricted surgical measures to the local condition. To make this decision is simple. It is only necessary to decide whether or not it will be possible to send the patient to the operating theatre with his diabetes adequately controlled. If it is possible, then the surgeon may proceed unhampered to apply whatever measures he thinks fit; if it is not possible, then his technique may require to be modified in the general interests of the patient. It is, therefore, necessary to have a clear idea of the clinical evidence which shows when control of the diabetes is *not* adequate.

An uncontrolled diabetic complains of the symptoms of thirst and frequency of micturition, and in addition he shows the signs of hyperglycæmia, glycosuria, and often ketonuria. The symptoms of diabetes are present only in cases which are grossly out of control, and their significance must be obvious to anyone. The minor degrees of inadequate control are revealed most clearly by the chemical signs. Of these chemical signs it is fashionable to regard a knowledge of the blood-sugar level as of most value. But unbiased considerations of clinical experience reveal that there is no definite correspondence between the height of the blood-sugar and the clinical condition of the patient, and that provided the control of the diabetes is satisfactory in other respects, an uneventful operative and post-operative course may be expected in diabetics even though hyperglycæmia is present. All the useful information that can be derived from a knowledge of the blood-sugar level can be obtained by testing the urine for sugar and noting, from the extent of reduction of Benedict's solution in different urine samples, the changes in degree of glycosuria. Glycosuria itself is not harmful, but a knowledge of the increase or decrease of glycosuria is of importance in guiding the administration of insulin. The most significant of the chemical signs is undoubtedly ketonuria, for according to its variation the clinical course of the case can be accurately forecasted. This sign is never found unless the diabetes is uncontrolled, and in its presence surgical measures are liable to have unfortunate sequelæ. It is detected in small degree by the nitroprusside test and in large degree by the ferric chloride test. Before a diabetic can be considered to be adequately controlled ketonuria must be absent, and it is of advantage if glycosuria has been reduced to the minimum possible amount.

Unfortunately these criteria of adequate control can be counterfeited. By starvation or severe restriction of carbohydrate the urine may be freed of sugar and sometimes ketonuria abolished. To institute such measures is to aim at satisfying chemical criteria of normality at the expense of the patient's general condition. I think most surgeons would agree that starvation is a poor preparation for operation

in non-diabetics, and there are no reasons for regarding it as a less harmful procedure in the diabetic. Fortunately, I think we can now take it is as a majority opinion that an adequate food intake must be maintained in the diabetic who is to undergo operation, and this being so the criterion of control previously stated can be accepted. *As long as ketonuria is absent a diabetic can be considered to be sufficiently controlled to support surgical measures and to have a normal chance of recovery.* This criterion indicates the principle of treatment which must be followed. In its broadest sense diabetes mellitus is a disease in which the ability of the body to utilize carbohydrate is impaired. When carbohydrate utilization is grossly restricted ketonuria appears. To abolish ketonuria carbohydrate utilization must be restored, and to do this carbohydrate must be given in adequate amounts with sufficient insulin to enable the diabetic to utilize this carbohydrate. The translation of this principle into therapeutic details can now be considered.

In diabetics requiring surgical treatment the physician is concerned with their pre-operative and post-operative treatment. From a practical point of view such cases may be divided into two groups ; those in which the operation can be undertaken at a chosen time after the patient has received a thorough preparation, and those in which the operation is an emergency and in which time allows only the minimum of pre-operative preparation. In either case the post-operative treatment of the diabetes is the same. The pre- and post-operative treatment of the former type of case will first be considered, and then the preparation of an uncontrolled diabetic for an emergency operation.

When several days are available in which to prepare an uncontrolled diabetic for operation, treatment differs in only one particular from the routine stabilization of diabetic patients. The point of difference arises because of the urgency of remedying the starvation in these patients which has resulted from the untreated diabetes. For this reason no attempt is made to build up the patient's diet from one of low to one of high calorie value. The patient is immediately given a diet yielding at least 1,700 calories and containing at least 180 grm. of carbohydrate. If he will take a larger diet, this is all to the good. Insulin is given in doses sufficient to abolish ketonuria and to reduce glycosuria to a minimum, and preferably in three approximately equal doses each day. It is inadvisable to commence zinc protamine insulin shortly before operation, as considerable time is usually required to determine its correct dosage. If the operation is to be done under local or spinal anæsthesia no further preparation is required, but if general anæsthesia is to be used special preparation is necessary. The following technique has proved satisfactory in my experience : On the day of operation the meal and insulin previous to the time of operation are omitted. Two hours before operation 50 grm. of sugar in lemonade are given by mouth and, just before the patient is sent up to the theatre, 25 units of insulin are given subcutaneously. If the patient has been stabilized previously with zinc protamine insulin the same preparation should be used if the operation is in the morning, but if it is in the afternoon, the usual breakfast and dose of zinc protamine insulin should be given and then, omitting lunch, the above preparation instituted, save that only 10 units of ordinary insulin are given immediately before operation.

The type of anæsthetic to be used is a legitimate concern of the physician because different anæsthetics vary in their liability to produce post-anæsthetic effects. For this reason the post-operative management of diabetics who have received local or spinal anæsthesia presents little difficulty. The non-volatile anæsthetics such as avertin and evipan also rarely give rise to trouble. Of the volatile anæsthetics gas and oxygen appears to be the best, but ether, by causing post-operative vomiting and thus preventing the patient taking food, may give rise to considerable trouble. I have had no experience in managing diabetics after chloroform anæsthesia but Joslin, who has had a considerable experience of its use, speaks strongly against it.

In the postoperative period the simplest case to manage is that of a patient who has had a cataract extracted under local anæsthesia. All that is required is to prescribe the patient's usual diet in a lighter form and, if necessary, to adjust the insulin in the same way as during routine balancing. The same simple measures will usually suffice after small operations performed under evipan anæsthesia. In the more serious cases, however, as after a major operation under ether anæsthesia, a special régime will be necessary, and this régime is planned to avoid two dangers, dehydration and diabetic ketosis. The former is treated by fluid and salt, the latter is prevented or cured by giving an adequate supply of carbohydrate and ensuring its utilization by means of appropriate dosage with insulin. No attempt is made to give a diabetic diet after a severe operation. If the patient can tolerate fluid by mouth he is given lemonade with sugar at frequent intervals and in addition allowed to take any other food or fluid he wishes. All urine specimens are tested as soon as possible for sugar and ketone bodies. If sugar only is present, insulin is given subcutaneously according to the following schedule: 20 units of insulin if eight drops of the patient's urine produce a red precipitate on boiling with one teaspoonful of Benedict's solution, 15 units if the precipitate is yellow, 10 units if the precipitate is green, and no insulin if there is no precipitate. Should, however, ketonuria be present as well as glycosuria, sugar, the antidote to ketosis, must be given in larger quantities by mouth, and in addition 25 units of insulin should be given at once and repeated after the ingestion of every 50 grm. of sugar. When the patient cannot take fluids by mouth these may have to be given parenterally. Provided ketone bodies are absent from the urine, no energetic steps need be taken for the first twelve hours after operation. During this time insulin should be given according to the schedule previously detailed, and a rectal drip of 5% glucose in half normal saline commenced. If post-anæsthetic vomiting is present steps should be taken to remedy this in the hope that at the end of twelve hours the patient will be able to take sugared drinks by mouth. If ketone bodies are present a slow intravenous infusion of 10% glucose solution in normal saline should be commenced and for every 50 grm. of glucose infused 30 to 50 units of insulin should be given, according to the severity of the ketosis. Usually an infusion of 2 to 3 pints will abolish a ketosis and this is the standard treatment for a marked ketosis occurring at any time after operation. At the end of the first twelve or eighteen hours if the patient still cannot take fluids by mouth such an intravenous infusion should be given, but if ketonuria is absent the covering dose of insulin for every 50 grm. of sugar injected need only be 10 to 25 units according to the degree of glycosuria present. Success in the post-operative treatment of diabetics depends upon close attention to the clinical condition of the patient and the state of his urine, so that any escape of the diabetes from control may be detected early and treated by the above simple methods before the condition becomes serious.

Up to this point we have been considering the management of a diabetic case in which the surgical lesion was such as to permit the time of operation to be chosen and to allow ample time for the patient to be prepared for operation. The treatment must now be considered of a case in which the surgical lesion requires urgent treatment and the time for preparation is limited. Under such circumstances the first question the physician has to decide is whether it is allowable to operate within an hour, the patient only receiving the usual preparation of 50 grm. of sugar in lemonade and 25 units of insulin subcutaneously. If ketonuria is absent or only present in such quantities as to give a slight nitroprusside reaction it is quite safe to operate as soon as possible. But if ketonuria is present in quantity operation should be deferred until it is either abolished or rapidly diminishing. In such cases an intravenous infusion of 10% glucose in normal saline should be started at once at the rate of one pint an hour and 50 units of insulin given for every 50 grm. of glucose injected. Frequent urine specimens should be obtained and tested for ketones. As soon as the

test for these has become negative or almost disappeared the operation can be commenced without further preparation. With the exception of hæmorrhage there are few surgical emergencies in which six hours cannot be spared to prepare the patient for operation in this way. In some cases, however, it will be found, at the end of six hours' treatment, that clinically the patient is not improved and the urine still contains large quantities of ketones. These cases are nearly always complicated by severe sepsis which in itself is hampering the measures taken to control the diabetes. Judgment is required, but as a rule it is best at this stage to deal operatively with the sepsis as rapidly and simply as possible and to continue the treatment with insulin and intravenous glucose during and after the operation. The post-operative treatment of these cases is effected by the same methods as have been described previously.

Certain special problems that arise in connexion with particular surgical lesions in diabetics can next be discussed.

It is well known that sepsis exacerbates diabetes and, by interfering with insulin action, handicaps the treatment of the diabetic condition. In my opinion patients whose diabetes is uncontrolled and who have a septic lesion, due either to the staphylococcus or the streptococcus, are unusually liable to develop septicæmia, and for this reason I urge that operation be undertaken early in such cases. In a case in which the sepsis prevents the physician establishing even temporary control of the diabetes there is unlikely to be any dispute as to the advisability of operation, but there is another type of case in which, the sepsis being milder, the surgeon may be reluctant to operate. The most frequent examples of this type of case are seen in patients with carbuncles, but they not infrequently occur in cases with wet gangrene of the feet. Such a patient is admitted with a large carbuncle and uncontrolled diabetes. The surgeon advises conservative measures for the carbuncle and the physician gains control over the diabetes in a matter of twenty-four or forty-eight hours. After this stage the majority of such cases do well, but in a few, two or three days later, it is found that despite the continuance of vigorous antidiabetic treatment the diabetes is beginning to escape from control. First profuse glycosuria and later ketonuria appear. This is evidence that the sepsis is spreading, and if the warning is neglected septicæmia is liable to follow. In any septic case after the diabetes has once been brought under even moderate control, then at the first sign of any breakdown of this control the carbuncle should be excised, or, in the case of gangrene, the affected extremity should be amputated.

One of the most interesting conditions which may bring the diabetic patient to the surgeon is the condition which has been called "the diabetic acute abdomen". The most prominent feature of this condition is severe continued abdominal pain of sudden onset associated with tenderness and rigidity of the abdominal wall. Usually the pain is felt most severely in the upper abdomen, but occasionally it is more marked on the right side. Such patients always show a strong ketonuria. The importance of the condition lies in its differential diagnosis from acute surgical emergencies, such as a perforated peptic ulcer or an acute appendicitis in association with diabetic ketosis. In making the diagnosis the history, if obtainable, is of value, but the physical signs associated with the surgical emergency may be mimicked so closely that reliance cannot be placed upon them. A further point of confusion lies in the occurrence of a leucocytosis in cases both of the acute septic abdominal emergencies and of diabetic ketosis. From a practical point of view the differential diagnosis is of little importance. Whether the condition is primarily due to a surgical emergency or to diabetic ketosis these patients are in no state to be operated upon, but by the time they are suitably prepared for operation the abdominal symptoms and signs will have ameliorated if the condition is merely a manifestation of diabetic ketosis. In my opinion the abdominal pain is probably due to distension of the liver by rapid accumulation of fat and is comparable to the pain that occurs over the congested liver in cardiac failure. It is noteworthy that the condition is rarely if ever seen in children.

Their livers appear to expand easily, for in children with diabetic coma the liver is usually greatly enlarged, whilst in adults in the same state great enlargement is seldom seen, but in both cases the liver is full of fat.

As the diabetic patient is usually under the routine care of a physician the prevention of surgical lesions is one of the physician's tasks, and in this field much may be done in preventing perforating ulcers of the feet and gangrene.

It is usually taught that a perforating ulcer arises from a diseased joint. I am in disagreement with this view. Until three years ago I had to act myself as chiropodist to the Diabetic Clinic at University College Hospital, and I was thus able to observe perforating ulcers at all stages of their formation. In the first stage the patient complains of a more or less painful callosity. On paring away the hard skin one exposes a small pear-shaped cavity, the base of which is against the callosity and the apex directed up into the soft tissues of the foot. The cavity is filled with a red fluid of the consistency of cream. X-rays reveal that the joints of the foot are not infected. I suggest that this lesion arises as the result of the callosity "focusing" pressure applied to the foot so that a colliquative pressure necrosis occurs in the soft tissues deep to the callosity. In diabetes this lesion appears to give rise to less pain than in non-diabetics, and perhaps this is the reason why often it is allowed to progress without treatment. At the second stage the cavity is still barred from the exterior by the callosity but has extended by the path of least resistance up into the soft tissues of the foot and surrounds, but does not enter the joint which is in relation to the callosity. The third stage is infrequently seen. Here the cavity has broken through the callosity but has not yet penetrated the joint. The lesion now has the external appearances of a perforating ulcer, but X-ray shows the joint intact and a probe passed along the track passes round the joint. The fourth stage is the familiar one in which a track leads from an infected joint through a perforation in the centre of a callosity to the exterior. In the first and second, and possibly the third stages, the condition can be cured by removing the callosity and applying wet dressings: in the fourth stage amputation at the diseased joint is often necessary. If this view of the development of a perforating ulcer is correct the preventive measures are clear. Treat all callosities in diabetics and perforating ulcers will not develop. Since Mr. A. J. R. Bride, of the Chelsea School of Chiropody, has put this measure into effect in the Diabetic Clinic at University College Hospital, no perforating ulcers have appeared amongst the patients under his care.

Gangrene, which is so common in elderly diabetics, may result from sepsis or from arterial disease. The tissues of the untreated diabetic seem handicapped in their resistance to infective agents so that infections which would rapidly be localized in the healthy person tend in the untreated diabetic to spread and even to cause massive necrosis of the tissues. The commonest example of this process in a pure form is that of the untreated diabetic, with no signs of arterial disease in the extremities, who has a cellulitis of the foot with gangrene around the site of infection, starting possibly from an infected corn. Perhaps it would be more accurate to classify these cases, not as gangrene, but as necrotising cellulitis. Gross arterial disease limits the blood supply to the tissues, and naturally this limitation is felt most in the peripheral tissues such as the toes. It is doubtful whether gangrene ever results from gradual restriction of blood supply due to progressive reduction in calibre of the arteries. It is more probable that gangrene in such cases is precipitated by thrombosis in a diseased artery occurring spontaneously or as the result of slight trauma or mild sepsis. The typical example of this process is the aged diabetic with the symptoms and signs of gross restriction of blood supply to the legs who is admitted with a dry gangrene of one or more toes. But in the great majority of cases of gangrene in diabetics both factors, that of sepsis and that of circulatory disease, play their parts, and this must be recognized in framing preventive measures.

The gangrene which is due to sepsis alone requires little consideration. It occurs only in untreated diabetics and consequently control of the diabetes is an efficient prophylaxis. It is the gangrene in which arterial disease is the main predisposing factor that presents the greater problem. It would undoubtedly be a wise prophylactic measure if all diabetics over 45 years of age were instructed in the simple hygiene of the feet and the avoidance of trauma. But there are some diabetics in whom arterial disease is so advanced that such measures are no longer prophylactic but of urgent necessity. Intermittent claudication, discoloration of the feet when dependent, cold feet with a dry scaly skin, all indicate the severity of the arterial disease and indicate the necessity not only of caring for the feet, but of inspecting the feet at frequent intervals to ensure that the instructions for their care are being observed. The services of a good chiropodist are of great value in this connexion as he will not only instruct the patient in the necessary prophylaxis, but will also carry out such routine measures as cutting the nails and trimming corns, measures which if performed inexpertly may well precipitate gangrene.

Lastly, there is one point which the physician will do well to bear in mind when gangrene has developed. Patients with advanced arterial disease deteriorate mentally and physically if kept in bed for long periods. If, therefore, the gangrene is dry and of minor degree a sandal should be fitted and the patient allowed to be ambulant. If the gangrene is more advanced and treatment by amputation a probability, no time should be lost in waiting to see if the part will separate ; the amputation should be performed and the patient got up and about as soon as possible. Although one may thus occasionally sacrifice a leg which might have been saved, it is in the general interest of these patients to operate early, for the majority have only a few years to live and confinement to bed will reduce this time still further.

Rules Issued to Patients for the Care of the Feet at the Medical Unit, Diabetic Clinic, University College Hospital

To avoid mortification keep the feet *clean* and healthy ; reasonably warm ; and prevent injuries or sores.

Rules for Care of the Feet

Every diabetic patient over 40 years should conscientiously observe these rules :—

(1) Wash the feet every night with soap and water. Dry gently but thoroughly, especially between the toes.

(2) Twice a week (or more often if ordered), after washing and drying, rub in lanoline thoroughly over the whole foot and the toes and all round the edges of each nail.

(3) If the nails are brittle and dry, soften them by soaking in moderately warm water for half an hour each night and then apply lanoline generously under and about the nails and put on an old pair of socks so that the lanoline will not be rubbed off by the bed-clothes. Do this each night until the nails are no longer brittle and then continue with Rules (1) and (2) only.

(4) Cut the nails only after soaking in soap and water and then cut straight across the top so that the edges cannot grow in.

(5) Wear thick socks. Women should either wear two pairs of stockings or one pair with ankle socks.

(6) Wear shoes of soft leather, preferably those in which the toe-cap is as soft as the rest of the " uppers ". *On no account* must the shoes be tight or pinch any part of the foot. The shoes should fit comfortably when you are wearing the socks or stockings advised above. Wear new shoes for half an hour on the first day and increase the time of wearing by one hour daily.

(7) Wear a warm pair of slippers when about the house, not shoes.

(8) If your feet are cold in bed wear bed-socks. If you must use a hot-water bottle see that it is in a blanket cover and outside the first layers of blankets so that you run no risk of burning

the foot. Do not toast your feet in front of the fire; avoid chilblains at all costs. If your feet get cold during the day wear more clothes. The best way to keep the feet warm is to keep the body warm.

Special Rules

(1) Corns, soft corns between the toes, bunions, and ingrowing toe-nails. Do not treat these yourself. Ask the doctor's advice.

(2) Treatment of injuries (cuts, blisters, &c.). Treat immediately. Buy some sterile gauze at the chemists and bandage this over the injury. Do not use antiseptics or disinfectants or hot fomentations. Come up to hospital and see a doctor as soon as possible and be sure to tell him you are a diabetic who has been warned to take care of the feet.

Rest, with the leg raised, as much as possible until the wound is healed. On the appearance of any pain, swelling, festering, or if the skin around the wound goes red or blue, get in touch with a doctor.

Appearance of Mortification

Consult your doctor immediately if any of the following signs appear in the *feet* or *toes* :—

(1) Either numbness or pain. (When either of these is present the toes often look as if made of wax.)

(2) Persistent blue or red discoloration.

(3) Blood blisters.

(4) A dark-coloured patch or scab.

Mortification may appear anywhere in the feet but the commonest place is at the edge of the nail, where it starts as a small dark scab from under the edges of which matter may ooze.

Dr. John T. Hunter (Anæsthetics): Examination of statistics compiled by Fitz of Massachusetts General Hospital in 1920 (*Medical Journal of North America*, 3, No. 4, 1107–1124) reveals a mortality rate of 30% in surgical cases suffering from diabetes. A recent work published by Hale and Tovell of the Mayo Clinic (*Surgery*, 3, Jan.-June 1938, 100–109), states that the mortality rate in 2,086 similar cases was as low as 3·3%.

It is undoubtedly insulin which has brought about this remarkable improvement in results. There has been great progress in anæsthesia during the past ten years. New agents and methods have been discovered and tested, and although these advances have done a great deal in rendering anæsthesia safe for the diabetic, the major portion of the credit is due to the discovery of insulin.

From the anæsthetist's point of view, the agent used must be one that has the least effect in the first place on the pH content of the blood, and secondly on the blood-sugar content.

Most diabetics requiring surgery are already under treatment by their physician, with or without insulin, and except in acute septic conditions are nearly always sugar and acetone free so far as the urine is concerned. These people, with certain adjustments of carbohydrate and fat intake, combined with a compensatory increase in insulin dosage during the twenty-four hours preceding the operation, will take their anæsthetic as well as if not better than many ordinary individuals. A number of patients unfortunately present themselves for the administration of an anæsthetic, who during the routine examination of the urine are found to be suffering from glycosuria and acetonuria. It is proposed to deal with these two groups separately.

(1) *Patients already under treatment.*—In pre-insulin days the only method available to render the patient fit for operation was rigid dieting, which in bringing his blood-sugar, fat, and acetone body concentration as near normal as possible, rendered his general resistance so low that it was a question as to whether the end justified the means. To-day, however, the diabetic takes his 120 or 140 grm. of carbohydrate

per diem, balanced by his dose of insulin, and he is as fit as the normal individual when he comes up for operation, sugar and acetone free.

It is now necessary to ensure that the patient has a generous store of glycogen to help deal with his anæsthetic.

One source of treatment recommended is to administer 80–100 grm. of carbohydrate at least five hours before operation, balanced by the patient's usual morning dose of insulin. Then one to one and a half hours before operation, 30 grm. of carbohydrate are given by mouth, followed by 15–20 units of insulin. If by chance the last 30 grm. of carbohydrate are wholly or partially lost by vomiting, the excess carbohydrate left over from the original 80–100 grm. will guard against hypoglycæmia.

In cases where the patient is taking zinc-protamine insulin, it is almost always in combination with ordinary insulin. Here the zinc protamine may be disregarded, and treatment carried out along the line already described. The danger of hypoglycæmia from the dose of zinc protamine insulin may be guarded against by administering 10% solution glucose in water *per rectum* by the drip method, 20 drops per minute for as long as he will retain it.

(2) *The untreated diabetic.*—The discovery of glycosuria during the urine examination does not carry so serious a significance as the presence of acetone. If this is so then every effort should be made to avoid an anæsthetic until adequate treatment renders the urine acetone free.

If, however, the surgical condition present makes immediate operation imperative, then the patient should be treated as for incipient coma. 40 gr. of carbohydrate are given four-hourly, with varying doses of insulin according to the amount of sugar found in the urine. Specimens must be obtained before each administration. If necessary the patient must be catheterized. Sugar +++ necessitates 40 units of insulin balanced by 40 gr. of carbohydrate. Sugar ++ requires 20 units of insulin against the same amount of carbohydrate. A trace of sugar requires only 10 units of insulin. This treatment is carried out until the patient is well enough to take a diet that can be properly balanced.

Premedication.—There is no contra-indication to small doses of morphia ($\frac{1}{6}$ gr.) combined with atropine $\frac{1}{100}$ gr. or omnopon $\frac{1}{3}$ gr. and scopolamine $\frac{1}{150}$ gr.; either injection may be combined with one of the barbiturates.

Avertin may be given, and probably has advantages over the other more rapidly excreted drugs in that its prolonged action renders it possible to keep the patient anæsthetized with nitrous oxide oxygen without the addition of ether. It may, however, hamper the rectal administration of glucose post-operatively, should the necessity arise.

The intravenous barbiturates are probably the most useful drugs used as basal narcotics. The best known of these are sodium evipan and sodium pentothal.

Choice of Anæsthetic

(1) *Local or regional anæsthesia.*—One or other of these is the method of choice in the diabetics, except in the presence of any sepsis. If it is essential to render the patient unconscious, nitrous oxide oxygen may be given or a small dose of sodium pentothal. It is better to use a regional nerve block rather than a complete infiltration of the area, because of the danger of sepsis. Hale and Tovell state in the paper already mentioned that there is a slight tendency to hyperglycæmia following this method due either to the slight toxic effect of the anæsthetic agent, or in cases where the peritoneal cavity is opened, to the subsequent fall in blood-pressure, usually about ten points.

(2) *Spinal anæsthesia.*—Diabetes itself is no contra-indication to the use of subarachnoid block. The method is useful in abdominal operations and in amputation of the lower limbs.

It may be said that it is superior to abdominal field block in that (*a*) the muscular relaxation is better; (*b*) the abdominal wall, whose tissues are possibly devitalized, is not infiltrated with large quantities of fluid.

It is contra-indicated in elderly, debilitated patients whose blood-pressure is unduly low.

Nitrous oxide, oxygen alone or combined with small doses of sodium pentothal, cyclopropane, or divinyl-ether, may be used as an adjuvant with advantage, especially in operations on the upper abdomen.

Agents used in spinal anæsthesia.—(*a*) *Novocain:* This is the least toxic of all. It may be used in crystalline form, dissolved in the patient's own cerebrospinal fluid, or in the form of planocaine. It is especially useful in the shorter surgical procedures such as amputation of the lower limb for gangrene. (*b*) *Percaine:* There are many methods described for the administration of this drug. The length of anæsthesia obtained by its use holds advantages over novocain in the more extensive operations. The two best-known methods of administration are those described by Howard Jones (*Anæs. & Anal.*, 9, 218), and Etherington Wilson (*British Jour. Anæsthesia*, 1934, 11, 43).

It is important in the case of the diabetic to avoid as far as possible any great fall in blood-pressure. This can be done by careful premedication. Morphia $\frac{1}{6}$ and hyoscine $\frac{1}{150}$ should be combined with coramine 1 c.c. at least three-quarters of an hour before operation. Ephedrine $\frac{3}{4}$ gr. to 1 gr. should be given ten to twenty minutes before the spinal injection. Careful watch should be kept on the blood-pressure every three minutes. Any tendency to deterioration can be checked by the intravenous injection of ephedrine in $\frac{1}{4}$ to $\frac{1}{2}$ gr. doses.

Neff and Stiles, in a paper written in 1936 (*Canadian Med. Ass. Journ.*, 35, 56–61) point out, however, that even with this method there is a post-operative rise in blood-sugar and a slight diminution of the CO_2 combining power of the plasma.

(3) *Inhalation anæsthesia.*—(*a*) *Chloroform:* There is no doubt that this drug must be avoided absolutely in all cases of diabetes. The tissue-cell destruction in the liver, caused by its toxic effect, impairs the glycogenic function more than any other agent. Now that we have such drugs as pentothal, divinyl ether, and cyclopropane at the disposal of the anæsthetist, the use of chloroform is totally unjustifiable.

(*b*) *Ether:* The value and safety of ether as an anæsthetic agent in diabetes are subjects for argument and consideration. Sansum and Woodyatt (*Journal Biol. Chemistry*, 1914, 19, 1) proved that ether administered to diabetic dogs produced immediate hyperglycæmia and temporary suppression of urine. Clinical observations show the same conditions arising in the human being accompanied by a rapid increase in the fat content of the blood, the whole process resulting in hyperglycæmia, glycosuria, and acetonuria. In practice, however, it is found that ether is of great value when used in small quantities as an adjuvant to nitrous oxide and oxygen, especially when the patient is receiving adequate pre-operative and post-operative treatment with glucose and insulin.

(*c*) *Nitrous oxide:* Nitrous oxide and oxygen mixture is undoubtedly the safest and best inhalation anæsthetic for the diabetic. McKesson, with his improved apparatus and technique of administration, accomplished much to widen the field of surgery possible under this anæsthetic when given alone. The effect on the blood chemistry shows a rise in blood-sugar greater, possibly, in cases where a degree of cyanosis has been necessary to keep the patient sufficiently deep. The tendency to

post-anæsthetic acidosis is negligible compared to ether. Nitrous oxide and oxygen can, however, be supplemented with sodium pentothal, divinyl ether, or cyclopropane, in order that relaxation may be obtained, together with adequate oxygenation to keep the patient a good colour throughout. An interesting paper was published in the *Lancet* (November 19, 1938, p. 1170) by Organe and Broad on the use of nitrous oxide oxygen in combination with sodium pentothal, a method that should prove safe and useful in diabetes.

Nitrous oxide oxygen is undoubtedly the safest anæsthetic to use in midwifery in diabetic patients.

(*d*) *Cyclopropane :* This, the latest inhalation anæsthetic, has superseded acetylene and ethylene in this country. Cyclopropane was investigated clinically by Waters of Madison in 1934. Examination of the blood chemistry following its administration showed a rise in blood-sugar, less than that following ether, which rapidly returned to normal. The CO_2 combining power of the plasma was not appreciably affected.

Stiles of Philadelphia, during his investigations into the effect of cyclopropane on blood chemistry, showed that in a series of 25 non-diabetic patients there was a rise of 8 to 30 mgm.% in the blood-sugar returning to normal in three to four hours. In 30 controlled diabetic patients there was an average rise of only 7 mgm.%, which also returned to normal in four hours.

The effect of cyclopropane on liver function was investigated by Raginsky and Wesley Bourne of Montreal in 1934. Experiments were carried out on dogs with normal livers and dogs with livers damaged by repeated administrations of chloroform. No increased impairment was found after administration of cyclopropane.

As far as renal function is concerned, it appears that excretion of urine is, as in the case of ether anæsthesia, slowed down or even suppressed. It rapidly returns to normal.

Blood-pressure is raised slightly, which is of great advantage when cyclopropane is administered in conjunction with a spinal anæsthetic.

It has been observed that cyclopropane anæsthesia is sometimes followed by an alarming fall in blood-pressure immediately after administration has ceased. Also it has been found that patients, although they have been free from nausea during the first twenty-four hours, suffer a great deal during the second twenty-four hours with retching and vomiting.

Neff and Stiles, in their paper already mentioned, point out that the former sequela is due to the too-sudden removal of the mask and consequent rapid drop in the oxygen concentration of the mixture inhaled.

Recent work published by Burford of New York (*Curr. Res. Anæs. Anal.*, 1938, 17, No. 5, 241, 251) on the uses of inert gases in anæsthetic atmospheres, suggests the value of nitrogen, helium, or hydrogen, in cyclopropane anæsthesia, or in any form of closed circuit anæsthesia, one of his points being that this fall in blood-pressure does not occur when the excess oxygen is replaced by one of these gases.

Recent experience has shown that this improved method of administration prevents these unpleasant symptoms.

Neff and Stiles, in the above-mentioned paper, also show a table demonstrating relative rises in blood-sugar and diminution in CO_2 combining power of the plasma in nitrous oxide oxygen anæsthesia, subarachnoid block by procaine, and cyclopropane.

	Blood-sugar	CO_2 Combining Power
Nitrous oxide	+ 4 mgm.%	− 3·7 vol. %
Subarachnoid block ..	+ 0·8 mgm.%	− 2·8 vol. %
Cyclopropane	+ 7 mgm.%	− 1·7 vol. %

These figures were taken three hours before operation following preliminary insulin and glucose dosage and four hours after operation, before post-operative treatment was started, in 90 controlled diabetics.

It would seem, therefore, that cyclopropane is a valuable agent for anæsthesia in diabetes, but still cannot take the place of nitrous oxide oxygen in minor surgical procedures.

(*e*) *Divinyl ether :* This new anæsthetic, when used in small doses, is useful in minor operations on children such as dental extractions, or tonsillectomy and adenoidectomy, guillotine method. It is also a useful adjunct to nitrous oxide oxygen when used in conjunction with a spinal or abdominal field block in operations on the upper abdomen. The absence of post-anæsthetic vomiting is a well-marked feature.

The effect on the blood chemistry is similar to cyclopropane, but in large doses it is toxic to the liver.

(4) *Intravenous anæsthetics.*—During the past eight years, various drugs for intravenous injection have appeared. Many of them vanished into obscurity quite rapidly, but some have come to stay, and form a necessary and invaluable part of the anæsthetist's armamentarium. Sodium-amytal, nembutal, and pernocton have been superseded by sodium-evipan, sodium-pentothal, and recently by yet another, sodium-thioethamyl. Of these the most popular is sodium-pentothal. This drug may be administered by the continuous method mixed with saline.

Experience with sodium-thioethamyl has shown very little difference between pentothal and thioethamyl clinically, except that possibly the latter has a slightly more depressing action on the respiratory centre. This method is excellent in diabetic cases as the resulting effect on the blood-sugar and the CO_2 combining power is very slight.

In conclusion it is proposed to append a list of operations, with suggestions as to the most suitable form of anæsthesia.

I.—*Minor operations,* including septic conditions, dental extractions.
Nitrous oxide oxygen.
Sodium-pentothal.

II.—*Ear, nose, and throat operations.*
Endotracheal nitrous oxide oxygen and pentothal or vinesthene.
Endotracheal cyclopropane.
Vinesthene in children for guillotine operations.

III.—*Ophthalmic operations.*
Sodium-pentothal (this is outstandingly useful in these operations owing to the absence of congestion, coughing, and post-anæsthetic vomiting).

IV.—*Thoracic operations.*
Nitrous oxide oxygen.
Cyclopropane.
Unilateralpercaine spinal (Pink and Harris).
The large area of infiltration necessary in local anæsthesia in thoracoplasty increases the danger of sepsis.

V.—*Abdominal operations.*
Abdominal field block.
Subarachnoid block in upper abdominal surgery, supplemented if necessary by nitrous oxide oxygen or cyclopropane.

VI.—*Amputation of leg.*
Subarachnoid block using novocaine.

The conclusions drawn from this short review point out that while insulin has done so much to render surgery safe for the diabetic patient, new methods and new agents in anæsthesia have also accomplished a great deal in preventing the post-anæsthetic complication that must, if possible, be avoided in diabetes, and that is acidosis.

Mr. E. C. B. Butler: I shall deal with cases of gangrene of the lower limb associated with proved diabetes. This condition is still one which should be looked upon as a grave complication, as despite the improved treatment now available the mortality at the London Hospital still stands at 21%.

The figures below show the results of the last 100 cases of diabetic gangrene as compared with 100 cases treated at the same hospital before the introduction of insulin.

Pre-insulin Figures

	Total	Alive	Dead	% mortality
Total	100	61	39	39
Males	70	46	24	34
Females	30	15	15	50
Deaths	39	0	39	100
Thigh amp. ..	35	22	13	37
Below knee	1	1	0	0
Syme's op.	2	1	1	50
Toe amp.	2	2	0	0
Per sym.	0	0	0	0
Medical treatment ..	60	35	25	42

Of these deaths 15 were from diabetic coma. The total operative mortality was 35%.

Ages	Total	Alive	Dead	% mortality
Under 50	16	9	7	44
50–59	33	20	13	39
60–69	40	26	14	35
70–79	11	6	5	45

Post-insulin Figures

	Total	Alive	Dead	% mortality
Total	100	79	21	21
Males	60	47	13	22
Females	40	32	8	20
Deaths	21	0	21	100
Thigh amp. ..	24	15	9	38
Below knee	6	5	1	17
Syme's op.	10	9	1	10
Toes	6	5	1	17
Per sym.	1	0	1	100
Med. treat.	53	45	8	15

Of these deaths there was no case of diabetic coma, the causes of death being divided amongst sepsis, bronchopneumonia, pulmonary embolus, and heart disease

Ages	Total	Alive	Dead	% mortality
Under 50	7	7	0	0
50–59	23	20	3	13
60–69	47	34	13	28
70–79	22	17	5	23
80–89	1	1	0	0

The total operative mortality was 28%.

In comparing these figures it can be seen that the use of insulin has apparently delayed the onset of gangrene so that its incidence now is at the same age level as that of the ordinary senile type. In addition it has abolished the deaths from coma

but seems to have had little effect on the death-rate from infection. It is interesting to note that the cause of death in two of the last series was gas gangrene from anaerobic streptococcal infection.

Finally, I should like to report a case which I had some years ago. A middle-aged woman was admitted having cut her wrist on some glass. She had severed her radial artery and her median nerve and had lost a lot of blood. She lapsed very quickly into diabetic coma, and although she was known to be a mild diabetic this was the first attack of coma she had had.

Her coma was treated in the usual way and then she was given a blood transfusion and lastly her median nerve was sutured under local anæsthetic. Here was a case of coma coming on as a direct result of arterial hæmorrhage combined with a certain amount of shock.

JOINT DISCUSSION No. 4

Sections of Laryngology and Odontology

Chairman—C. A. Scott Ridout, M.S.
(President of the Section of Laryngology)

[*March* 3, 1939]

DISCUSSION ON ANTRAL INFECTION OF DENTAL ORIGIN

A. T. Pitts (Section of Odontology): There seem to be three possible ways in which infection of the antrum may arise from a dental cause. The first is the result of chronic dental infection, the second of acute dental infection, while the third is the result of an accident in the course of dental treatment whereby the antrum is opened.

All my clinical experience is negative with regard to the first. I have not had any cases which suggest that as a result of chronic dental sepsis an antral infection follows. The experience of my colleagues also seems to be negative, but I am not prepared to say that this negative clinical experience is conclusive. If such infections of the antrum could occur in all probability they would not show themselves until after a long interval. There would be nothing to show the dentist that an antral infection had arisen as the result of chronic dental sepsis.

The two forms of chronic sepsis in the teeth are pyorrhœa and apical infection leading to a granuloma which can be seen by X-rays. I imagine that if antral infection arises it would be much more likely to do so in connexion with pyorrhœa, for in this condition the supporting tissues are affected. The bone is infected and becomes softened, and on *a priori* grounds it seems likely that a seepage of infection through the antral wall could follow, but clinically I have no evidence that this is a common cause of infection of the antrum.

The acute dental infections cannot be regarded as common sources of antral disease. The pus can escape more readily from an acute dental abscess in other directions than through the floor of the antrum. I have not had experience of such a case.

Dental cysts, although they grow commonly in the region of the antrum, rarely open into it. They push the antrum upwards and the bony floor is eroded, but the lining remains intact. It is important in dealing with such cysts to prevent the antrum from becoming infected by avoiding an opening into it, and for that reason curetting of the deeper part of the cyst is contra-indicated. If an opening be made large enough into the dental cyst there is no need to remove its lining.

If the cyst has extended into the antrum it becomes a matter for the rhinologist and not for the dental surgeon. The commonest way in which the antrum becomes infected is either when it is opened in the course of extraction or when a tooth or a root is pushed into it as the result of a dental operation. It is by no means uncommon for the antrum to be opened in the course of an extraction, since the antrum is in relation to all the molar teeth, the premolars, and sometimes even to the canines. This accident has happened to me mostly in connexion with the molars. It is a commonplace amongst dental surgeons that when such an accident occurs the opening into the antrum should be left alone. At the most a stitch should be inserted.

When the antrum is opened by the extraction of a third molar the tuberosity comes away with the tooth. In these cases the antrum has extended into the tuberosity and hollowed it out. There is a good chance that the opening into the antrum will heal up without any infection. In a few cases, however, the antrum becomes infected, particularly if the patient uses a mouthwash vigorously or blows his nose forcibly, or if any syringing or probing has been done.

The second way in which an antrum becomes infected is when a root is pushed into it during a dental operation, and this is one of the commonest causes. I have not had many personal experiences of such cases, but I have had three within a comparatively short time. Two of them were cases where there were no teeth present but merely a small root very close to the antrum. I tried to lift the root away, but I was unlucky enough to push it into the antrum. I was able, however, by using the sucker to remove the root. If this accident happens to a dentist he is fully justified in making a brief attempt to remove the root, but prolonged efforts are not justifiable. The case should be referred to the rhinologist so that the antrum can be deliberately opened. In my experience infection follows in most of these cases. Of the two that I have just mentioned in one the opening healed perfectly well, but in the other the antrum became infected, it had to be washed out through the nose, and a fistula was left, though later this healed and closed without the need of any plastic operation.

I am opposed to opening the antrum through the socket of the tooth and putting in a vulcanite plate with a plug. Probably it is unnecessary to make such a statement because to any rhinologist it would be an abhorrent method. But I recall the experiences of my student days in which the deliberate opening of the antrum through a molar socket was considered one of the operations of dental surgery. I have merely mentioned this to indicate my view that treatment of the antrum by drainage is not in the province of a dental surgeon but in that of the rhinologist.

E. A. Hardy: The antrum, although connected anatomically and pathologically with the mouth, is not a joint field of action for the nose and throat and the oral surgeon. However much the thickness of the floor of the antrum varies, the bone is always very thin and could easily be encroached upon; but the oral surgeon only touches it by accident, whilst the nasal surgeon has abandoned the old Cowper operation of drainage through the tooth socket (rightly described by Vorhees as the worst operation in surgery; though it is still not without its advocates).

Reference to literature on the ætiology of antral disease reveals a wide diversity of opinion. Clinical statistics attribute from 8% to 50% of cases to oral, rather than nasal, origin. I. Brophy, supported by Oakman (1914), gives 85%; Gordon Berry, before the American Laryngological Association in 1928, gave 25% for the acute and 50% for the chronic. Whatever the proportion may be, surgeons should not only diagnose the condition, but determine the cause. Infection from the mouth will never be cured by lavage alone, nor will nasal infection be cured merely by extraction of teeth in relation to the antrum (Christiansen, 1935).

The existence of disease once established, it remains to determine the origin. Cacosmia is one of the signs and symptoms pathognomonic of an oral origin (Fairbairn, 1933), though it so often leads the patient into the hands of the nasal surgeon. Myles Formby, in the *British Dental Journal* in 1934, described concisely four possible ways of oral infection. (1) Direct injury and rupture of an alveolar abscess usually the first or second molar (*see* fig. 1); (2) tissues infected in the following order: dental caries, apical infection, mucosa infection, empyema of antrum; (3) blood and lymphatic streams—these are possible, but unlikely. If in the blood-stream, the organisms would also travel elsewhere; and the lymphatic stream flows away from the antrum towards the pterygoid, submaxillary and deep cervical glands; (4) infection of mucous membrane surfaces from pyorrhœa—this is described

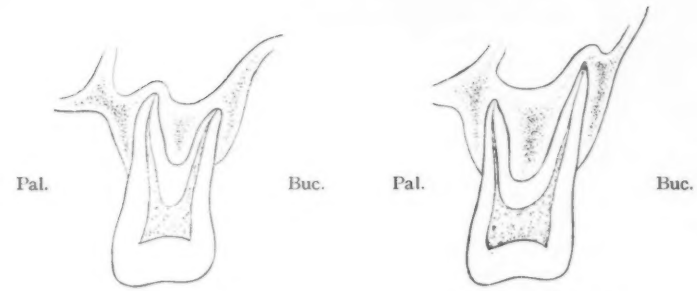


FIG. 1.

by him as via the lymphoid tissue in the nasopharynx, producing ethmoiditis, obstruction of nasal breathing and of ciliary action, and, later, empyema. But direct infection through the bone seems to me more likely.

Treatment.—Prophylactic: This is the particular concern of the oral surgeon. If trauma occurs owing to a fractured molar root, Dr. MacMillan of Cincinnati (1926) has described a good method of extracting the apex, without interfering with the membrane. If the membrane is perforated and the molar apex pushed into the antrum, the apex can be left there, or the socket can be enlarged and a looped piece of wire used to hook it down. The method mentioned by Mr. Pitts of suction with a blood sucker or saliva-ejector sounds excellent. The socket must in each case be covered with a plastic flap. Irrigation should never be used to bring an apex down or to wash away the pus. Irrigation through the alveolar fistula should always be condemned.

The flap is the same as that used to close an alveolar-antral fistula (*see* fig. 2).

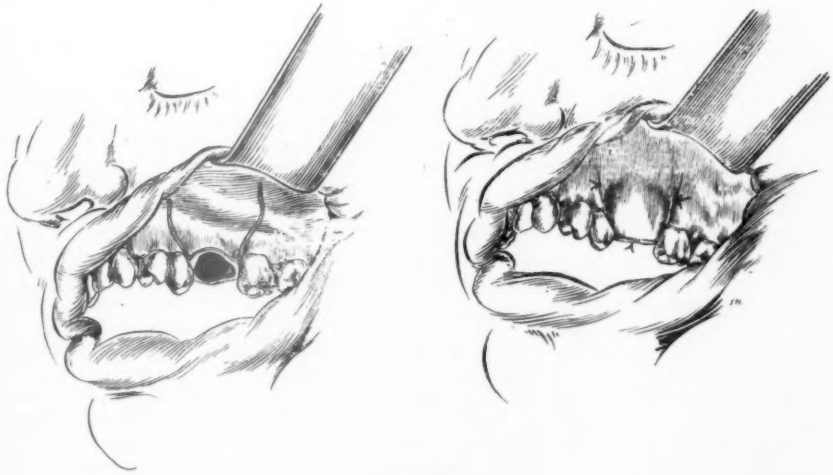


FIG. 2.

Two incisions are made over the roots of the adjacent teeth, beginning at the gingival margin and diverging upwards to the reflection of the mucous membrane and continued upwards at a less divergent angle, for a distance equal to the width of the socket. The flap must be carefully dissected from the bone, as the mucoperiosteum, being friable and tough, is easily split. The linguo-gingival margin is then freshened with knife, cautery or spoon, and the flap sutured into place with 3 or 4 sutures. Silk should be used on eyeless eye-curved needles, Nos. 3, 6, or 28. Although the mucoperiosteum is tough, a round-bodied needle, less likely to cut out, is best. Deknatel silk is stronger than any made in this country, and No. C is recommended. For use with the flap, tissue hooks are preferable to toothed forceps; they are useful too in helping the needle through the tough edges. If attention is given to the details of this process, a vulcanite plate is never needed. If the suturing should leave any part uncovered, "Wondrpak" will stop food debris getting into the wound.

With this method a fistula is unlikely to develop, even when an apex is allowed to remain.

Do all rhinologists insist on extraction of all dead teeth? If not, how do they assess the importance of a particular focus as a cause? The extraction of a front tooth might condemn the patient to a life-long denture.

Alveolar fistula.—Successful treatments are recorded by E. P. Weih (1930) with the actual cautery, followed by trichloracetic, twice a week.

The use of the silver wire drainage tube and the vulcanite plug on a denture have been responsible for the numerous fistulæ that used to be seen. Now that this practice has been abandoned and the plastic flap substituted a fistula is unknown.

The plastic flap, as described under the heading of prophylactic treatment, effectively closes these fistulæ after cauterization.

BIBLIOGRAPHY

Christiansen, G. (1935), *J. Am. Dent. A.*, **22**, 1926.
Fairbairn, J. (1933), *ibid.*, **20**, 1269.
Formby, Myles (1934), *Brit. D. J.*, **57**, 582.
MacMillan, H. W. (1926), *Proc. 7th Internat. Dent. Cong.*, 1107.
Oakman, C. H. (1914), *Proc. 6th Internat. Dent. Cong.*, Sect. II, 1.
Thomas, C. Hamblen (1932), *J. Laryng., Otol.*, **47**, 470.
Weih, E. P. (1930), *Ann. Otol., Rhin., and Laryng.*, **39**, 533.

A. J. Wright (Section of Laryngology): Much attention has been devoted of late years to the pathology of cases of nasal infection of the accessory sinuses. In addition, as a result of investigations into the normal physiology, particularly the activity of the ciliated epithelium—a subject recently brought before us by Proetz, *Proc. Roy. Soc. Med.*, **31**, 1405 (Sect. Laryng., 45), at the Summer Meeting of this Section last year—a more conservative line of treatment is developing. Little attention, however, seems to have been paid to the problem presented by cases in which infection of the maxillary antrum has a dental origin, there is uncertainty in our present ideas concerning the pathology with a corresponding uncertainty as to the most satisfactory treatment. Possibly this is due to some extent to the fact that the alveolus with its teeth and the antral cavity are separately in the charge of two different departments of surgery. If this be so, then to-day's combined discussion is justified.

Pathology.—Established factors in the pathology are, I believe: Infection may involve the antrum as the result of a spread from the apex of a tooth with an infected pulp, with or without the occurrence of cyst formation. Brown Kelly many years ago gave a detailed study of dental cysts and allied conditions which still stands, with the possible exception that the rare dentigerous cyst might be simply regarded as a dental cyst which has included an unerupted tooth during its expansion rather than as a developmental abnormality (*J. Laryng. and Otol.*, 1922, **37**, 433). Apart from the spread of infection from an infected pulp, it is perhaps not

always so well recognized that periodontal disease may also frequently spread to the antrum. In addition, the infection which occurs round a tooth fragment left in the alveolus or an unerupted tooth may produce the same results, as may the accidental opening of the antral cavity during an extraction. The extent to which disease in the bone of the alveolus is an important part of the clinical condition is at present ill-defined but I suggest that in many cases an alveolar osteitis is the essential condition and that any infection of the antral lining is secondary to this and will persist until the bone infection resolves. The comparative study of the skiagrams of cases of dental and nasal infections of the antrum seems to me in many cases to show that in the former case the lesion is an ascending alveolar osteitis with chronic inflammatory changes which are largely confined to the alveolar recess in the antral floor. This view of the pathology seems to be frequently confirmed by the condition found when the cavity is opened through the canine fossa, granulations being present in this recess with a relatively normal lining in the upper part of the cavity. Another uncertain factor in pathology is the degree to which a combined dental and nasal infection is responsible for the clinical picture presented. Not infrequently a nasal infection will produce a flare-up in, and draw attention to, an antrum which had been previously the seat of old-standing dental infection in its floor. Another uncertain factor in pathology is the frequency of the occurrence of an ascending infection from the antrum to the ethmoid and frontal sinuses in cases of dental infection. I was formerly of the opinion that such an occurrence was a rare one but I am now doubtful as to whether this was not a mistaken view.

Diagnosis.—The established methods of clinical examination with transillumination and radiography, combined if necessary with puncture, are on the whole satisfactory. Antral infections are, however, not infrequently latent, the error then occurring in the direction of not considering the possibility of its existence rather than in any difficulty in establishing the diagnosis, if it be sought for. Very frequently some degree of postnasal discharge and morning cough with some general unfitness makes up the whole of the clinical picture as far as the patient is concerned. It might also be mentioned that an edentulous jaw does not necessarily rule out the possibility of a dental infection of the antrum having occurred before the extraction of the teeth, however long before. Possible errors in the use of proof puncture in the presence of a dental cyst are well recognized.

Treatment.—Prevention is usually possible but cure may be difficult or impossible. In the great majority of cases, disease exists in teeth or alveolus for a long period before the spread of infection to the antral cavity. While rhinologists are learning that progress lies in conservation rather than mutilation as far as the nasal sinuses are concerned, the dental surgeon appreciates more and more that efforts at preserving the infected tooth, while a monument to his technical skill, are not infrequently to the patient's detriment. I suggest the following points for discussion :—

(1) Prevention. Is it wise to adopt a conservative line of treatment in cases of infection in, or around, the upper premolars and molars ?

(2) What steps, if any, should be taken in the event of an opening of the antral cavity during the extraction of a tooth, as shown by discharge of blood from the nose or the passage of liquids into the nose ? I suggest expectant treatment, with the avoidance of any syringing of the socket.

(3) What steps should be taken should a tooth or fragment unfortunately be displaced into the antrum ? I suggest that it should be removed through an opening in the canine fossa at an early date, as infection always supervenes if it be left as a foreign body in the antrum.

(4) What steps should be taken in regard to a fragment of an upper premolar or molar retained as a result of fracture during extraction ? Whatever else is done, the patient should always be informed so that in the event of any symptoms arising its presence may be known.

(5) When there is a search for infection in the upper teeth or alveoli as a cause of constitutional symptoms the condition of the antrum should also be ascertained. Thus, I have on several occasions observed patients with joint or other lesions in whom a dead infected molar tooth, perhaps with apical disease, had been dealt with, but the co-existence of an antrum full of pus in close relationship to it had been unrecognized.

(6) If we are presented with the problem of an infected maxillary antrum with one or more infected teeth which are probably responsible, what course should be followed ? Should the teeth be removed and an interval allowed for the possible resolution of the antral infection, or should teeth and antrum be treated surgically at the same time ?

In designing operative measures for the antral suppuration, what should be our objective as far as the cavity is concerned ?

(*a*) If the antrum be opened through the canine fossa, the incision should be made low down on the alveolus and particular attention should be paid to the alveolar sulcus. Unless grossly diseased, the remainder of the antral lining should be preserved.

(*b*) Has an alveolar opening through a tooth socket still a place in the surgery of dental infections of the antrum ? Or should openings between the antrum and the mouth be allowed to close as soon as possible.

(*c*) As far as intranasal interference is concerned, in view of the researches of Proetz and the observation that dental infections tend to be confined to the alveolar sulcus, should not such intranasal interference be chiefly directed towards drainage and ventilation in the middle meatal region by any necessary reduction of the middle turbinal or opening up of ethmoidal cells ? In my experience, a large opening in the inferior meatus has its drawbacks while a small one tends to close rapidly.

E. D. D. Davis said that he had been associated with the Royal Dental Hospital for a number of years, and formerly one of the commonest causes of antral infection was considered to be an alveolar abscess or the presence of dead teeth. The facilities for dental treatment had now been so much improved that this condition was rarely seen. What occurred nowadays was a septic extraction—a difficult extraction causing sepsis—followed by infection of the antrum. Another accident but rarely seen was suppuration of the antrum following the operation called alveolectomy.

Opening of the antrum by extraction of teeth was a common occurrence, and a glance at the floor of the antrum showed how easy it was to do so. It was like taking the cork out of a bottle. There were very few dental surgeons of experience who had not opened the antrum at some time or other. The patient should be told beforehand that it was quite easy to open the antrum and that this was one of the risks of extraction of a wisdom or upper molar.

Pushing the root into the antrum usually resulted from fracture of the apex of the root. The dental surgeon was naturally anxious to extract that apex, and so his forceps either went into the antrum beside the root or he pushed the root itself into the antrum. There was no reason why he should not leave that root, which in many cases would come to the surface later and could be extracted more easily. If it were suspected that the root had been pushed into the antrum it was important to be sure that it was actually there. If the root was in the alveolus, X-ray photographs would show it to be vertical, if it was in the antrum it would be lying more or less horizontal and at a higher level. He was opposed to enlarging the opening in the aveolus because of the fistula that might result, and so in a number of these cases he had had to open the antrum from the canine fossa and take out the root. He had not yet made up his mind whether that should be done as an emergency operation at once, or whether the case should be allowed to wait. There was usually an enormous amount of œdema of the mucous membrane of the antrum after the

tooth had been driven into it, and if one waited a little before opening the antrum that œdema would have disappeared and the root would be found either lying on the floor of the antrum or some distance above it. In more than one case he found the root actually in the middle meatus of the nose, probably carried through the natural ostium by ciliary action. It would be seen how difficult it was with the œdema of the mucosa of the antrum to carry out effective syringing, with the natural ostium closed by œdema. The operation for an antral suppuration of dental origin was much more successful than in an antral infection of nasal origin where other sinuses might be infected. The percentage of cases in which the antral suppuration was of dental origin was a little less than 20%, but his own figures were high for dental cases because he received a number of these cases from the Royal Dental Hospital.

Dental cysts were of two types. One was the small cyst in the front part of the mouth which the dental surgeon converted into a saucer-shaped cavity, and this healed perfectly. But in the other form of cyst, in the molar region, there was likely to be encroachment on the antrum. If the cyst was opened from the mouth it could be packed for weeks or months and the cavity still remained. On the other hand, if the party wall between the antrum and the cyst be removed, and the cyst and antrum converted into one cavity, and then drained into the nose, it would heal in about three weeks. He had watched one case of this kind for three years and the patient had not had any trouble since the operation. Others also had good results with this method as against drainage of the cyst into the mouth.

Draper Cambrook said that Mr. Hardy had mentioned the flap operation. To deal with flaps was often very difficult. He saw a case a month or two ago, in an edentulous patient, and there was in this region an area of about the size of a sixpence in which the lining of the membrane of the antrum was showing. The patient had had an extraction, which must have been a very rough one, because the bone had been completely removed over this area. He took two flaps, one running forward and one on the cheek side running backwards, and they held together perfectly well.

H. H. Stones said that there were one or two points that Mr. Pitts had made which he wished to corroborate. He entirely agreed that dental surgeons saw very few cases of infection of the antrum of which they could be certain that the origin was dental. Personally, he had seen about three or four cases arising from an acute apical condition, but none from the chronic side.

A few years ago he carried out experiments on the alveolar bone in pyorrhœa, and found that the bone immediately under the alveolar crest was infected only in 15% of cases in man. Arising out of that he would suppose that the possibility of the infection of the antrum in these chronic parodontal infections was rather remote.

On the subject of apical granuloma, they had been told by experienced bacteriologists that a pulpless tooth was always infected irrespective of the radiological findings. On the other hand, it is known that around the little area of rarefaction sometimes seen at the root there was an intense round-celled infiltration, and one rather wondered to what extent this acted as a barrier.

He wished to ask two questions of the laryngologists. Should a piece of tooth be pushed into the antrum during an extraction one method of dealing with it is to enlarge the opening of the alveolus at once and remove it by syringing out through the mouth, but he considered Mr. Pitts's suggestion of using suction was very much better. He wondered what the laryngologists thought of the former method as to a certain extent micro-organisms were introduced if syringing took place through the mouth. Further, in case of chronic infection, when the surgeons operated through the canine fossa did they invariably make an antronasal opening as well ?

W. A. Mill said that it had been most interesting to hear how the members who had spoken for odontology regarded infection of the antrum from dental causes as uncommon. He had read in literature various figures giving the extent to which maxillary sinusitis was supposed to be due to dental infections, but he had to confess that in his own experience he had not found infections of the teeth giving rise to maxillary sinusitis, except, of course, in those cases in which accidents had happened. There was one case he remembered where, in curetting the lining of the antrum, he opened what he imagined was an abscess at the root of the tooth. That did seem to be a case of definite dental infection.

He had been interested in the opinion that a dead tooth was always infected whatever the X-ray picture might say. He had on occasion been convinced that teeth were the cause of the symptoms, but on having them X-rayed no infection was indicated ; yet the symptoms, such as pain in the ear and in the face, persisted. He thought that in some cases the X-ray picture had been misleading in this respect.

Mr. Mill added that when the Caldwell-Luc operation was carried out an opening was always made into the nose.

E. A. Hardy said that he had been asked about the technique of flap operations from the cheek side. In such cases one had a very large amount of mucous membrane to play with, and if required one could extend the incisions quite a long way on to the cheek. Later on, in order to fit a denture, one could do an epithelial inlay if necessary, and restore the buccal sulcus. He tried to avoid touching the palate as much as possible, because the resulting scar tissue was rather thin and any denture worn over this tended to rub it away, and the surrounding tissues became inflamed very easily.